Leading Article

# TCDD Biomonitoring and Exposure to Agent Orange: Still the Gold Standard

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### Introduction

The development of increasingly sophisticated methods for biomonitoring of low levels of chemicals in human tissue is rightly regarded as one of the premier achievements of environmental science, and it is widely regarded as the 'gold standard' for assessing actual received doses in persons exposed to environmental chemicals [1]. The investigation of the dioxin contaminant in Agent Orange is one of many striking examples where the potential exposures of various populations, previously uncertain, were clarified by biomonitoring of actual levels in human tissue [1]. In 1977, as one of the first volunteers for monitoring of TCDD in adipose tissue, I experienced the power of the technique first hand. What I learned was that I had an ordinary background level of TCDD like most people, notwithstanding my years of research and fieldwork on Agent Orange [2]. My exposure had been primarily through collecting and handling biological and environmental samples, and not by direct contact with the liquid herbicide.

Thus, it was with some surprise that I read a report by the Institute of Medicine Committee (IOM) on the Assessment of Wartime Exposure to Herbicides in Vietnam approving a proposed methodology for estimating exposure to dioxin and Agent Orange in Vietnam without validation by analysis of serum dioxin levels [3]. While such validation was specified in the research proposal, the Committee agreed with its principal contractor on the research to abandon serum dioxin analysis after initial results were uniformly negative and went on to suggest that such analysis was no longer useful in studies of Vietnam veterans due to the passage of time [3]. At about the same time, the contractor for the IOM Committee work on Agent Orange exposure published an article concluding that dioxin and herbicide exposure in Vietnam were much greater than reported by all previous investigators, based on computer modeling and assumptions underlying a calculated exposure opportunity index that were unsupported by actual measurements of serum dioxin levels [4].

While the major epidemiological studies of Vietnam veterans and Agent Orange have attracted considerable attention over the years, the important questions of exposure and actual absorbed dose had kept a lower profile until these recent publications. I, and others familiar with the extensive prior work on exposure to Agent Orange, were prompted to re-evaluate the issue in light of these new publications, and our work will be presented in a series of articles and commentaries in forthcoming issues of ESPR (see the overview on p. 146). My conclusion is that the IOM Committee's approach to exposure assessment is ill conceived, and fundamentally flawed. Serum dioxin analysis remains the gold standard, and the failure to validate the model ultimately endorsed by IOM should have led the IOM committee to question the validity of the methodology rather than to drop serum dioxin analysis from the project.

Numerous studies relying on extensive serum dioxin testing have established that some RANCH HAND (the Air Force unit responsible for spraying herbicide from fixed-wing aircraft) and the US Army Chemical Corps veterans involved in the application of Agent Orange in Vietnam had absorbed doses of dioxin that can still be distinguished decades afterwards [5,6]. Similar studies of ground troops have not found elevated levels of dioxin – strong evidence that these troops were not significantly exposed to dioxin in Agent Orange [7]. The following summary of studies of biomonitoring of dioxin levels from Agent Orange exposure, and the broader public policy context, will provide an introduction to the issues to be addressed in detail in forthcoming papers.

### The Centers for Disease Control Serum Dioxin Study

The 1988 serum dioxin study by the Centers for Disease Control and Prevention (CDC) compared levels of serum TCDD in 646 US Army veterans who served as ground troops in the most heavily sprayed regions of Vietnam with those of 97 Vietnam-era veterans who had not served in Vietnam [7]. The distributions of TCDD levels were 'nearly identical' in the two groups, both having means and medians of about 4 ppt TCDD, which was well within the range of background at that time. The CDC conducted an extensive analysis of self-reported exposure histories, herbicide spraying records, and military records (five different computed Agent Orange exposure scores using dates and map coordinates of herbicide sprays, military unit locations, and dates of service for each Vietnam veteran) to determine whether there might be a relationship between these surrogates of exposure and the measured serum TCDD levels in the Vietnam ground troops. None was found.

Neither military and spraying records nor self-reported history of exposure could reliably identify high or low exposure groups, and "most US Army ground troops who served

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in Vietnam were not heavily exposed to TCDD, except perhaps men whose jobs involved handling herbicides" [7]. These results were consistent with other studies and so clear cut that a planned epidemiological study of ground troops and Agent Orange was discontinued as infeasible.

Subsequent CDC investigations of health effects in ground troops focused on whether the overall 'Vietnam experience' had increased the risk of cancer or other diseases [8,9,10,11]. These studies identified a number of health effects associated with military service in Vietnam. Other studies checked whether such effects were related to secondary indicators of possible exposure to Agent Orange [12,13,14]. No such relationships were found. For example, one study reported an excess of non-Hodgkin's lymphoma in a cross-section of various American forces serving in Vietnam, but the excess was found to be greatest in 'blue water' Navy serving offshore, and there was a deficit of cases in ground troops in heavily sprayed areas [15].

Other investigators conducted extensive epidemiological studies of the RANCH HAND and Chemical Corps veterans, many of whom routinely handled Agent Orange in Vietnam and had elevated serum TCDD levels long after exposure [5,6]. Studies of the RANCH HAND and Chemical Corps veterans are continuing. Even as recently as 1997, the distribution of serum TCDD levels still clearly demonstrates that substantial numbers of these veterans were exposed to Agent Orange, though many individuals have levels now at background. The results of these studies of verifiably exposed veteran populations remain essentially negative [16]. None of these veterans has been confirmed to have had chloracne, a skin disease characteristic of substantial TCDD exposure found among industrial workers with serum dioxin levels generally much higher than those of RANCH HAND and Chemical Corps veterans [16,17].

#### Validation of Exposure with Serum TCDD Levels

Testing of serum dioxin levels has been widely regarded as the gold standard for epidemiological studies of Agent Orange and dioxin since its development in the 1980's. Although such testing is expensive, the major industrial studies since the 1980's have employed it to validate various methodologies for estimation of exposure. Many more studies simply relied upon serum TCDD levels to measure exposure to dioxin-containing materials. While the passage of time complicates the use of serum TCDD results, it remains the best possible evidence of an historical absorbed dose of TCDD. Its superior predictive power has been confirmed repeatedly; for example, in the observation of chloracne in those individuals with the highest serum dioxin levels, but not in Vietnam veterans who are the subjects of the RANCH HAND and Chemical Corps studies [18].

In light of the extensive scientific consensus that serum dioxin analysis is the gold standard against which exposure models are tested and validated, the IOM Committee's recent decision to waive such validation in a study of Agent Orange exposure merits close examination. To explore the possibility of conducting studies along the lines of those discontinued by CDC, the IOM in 1997 established the Committee on the Assessment of Wartime Exposure to Herbicides in Vietnam, which contracted for the development of a methodology for characterizing exposure of veterans to Agent Orange in Vietnam [19]. The contractor, Columbia University's Mailman School of Public Health (Dr. Jeanne Mager Stellman, Ph.D., Principal Investigator), developed a methodology for calculating an exposure opportunity index on a given date and location in Vietnam based on historical reconstruction of herbicide spraying activities and other military records [20].

The IOM contract specified for the model to be validated using serum dioxin testing as in other major studies. However, in initial tests "a high percentage of samples had dioxin levels below limits of detection" and "the remainder were at or near background." These results led to "serious concerns" that further studies to validate the exposure opportunity index with serum dioxin levels in veterans "would be dominated by false negative assays." "Accordingly, and with the concurrence of the Advisory Committee, [the contractor] canceled the serum study..." [21]. In 2003, the IOM Committee endorsed the model without validation by serum dioxin analysis and recommended that the Department of Veterans Affairs fund a 'non-governmental organization' to conduct epidemiological studies using the model [3]. The IOM Committee stated that serum dioxin results would not have been reliable because "too much time has passed since exposure" [3]. Recently, lower background levels in the population have been reported, and this lowering has allowed detection of previously elevated levels that would not have been possible with background levels in the past [22].

#### The Continued Necessity of Verification

It is surprising that the IOM Committee would depart from established research methods so readily and without acknowledgement of the radical step it was taking. Their reasoning seemed to have been that their exposure methodology *might have been* reliable and yet fail serum dioxin verification due to the passage of time. But the IOM Committee concluded that the exposure methodology actually *is* reliable. At bottom, the IOM Committee simply assumed that troops who served in the closest proximity to Agent Orange spraying in Vietnam *must have been* more exposed than those distant from the spraying.

As appealing as that assumption may seem in the abstract, it is flatly inconsistent with the extensive data reported in studies such as the 1988 CDC Serum Dioxin Study [7], the extensive historical record of military herbicide operations in Vietnam [23], and well-established research into the environmental fate and bio-availability of TCDD under the conditions present in Vietnam [24,25]. Exposure models quite similar to that now proposed by the IOM Committee were

thoroughly tested in the 1988 CDC study and found to be poor predictors of absorbed dose of TCDD. The earlier models could not distinguish between serum dioxin levels in ground troops with the highest potential for exposure and those with negligible potential exposure – at a time closer to the original exposure.

#### New Data on Agent Orange Exposure

The issue of exposure of veterans to Agent Orange has become more prominent because of the IOM Committee's abandonment of serum dioxin analysis to verify the exposure model and the contractor's report that exposure to dioxin and Agent Orange was much greater than previously reported based solely on the exposure opportunity index from the model. The model relies on accuracy of military records and on assumptions about the fate of dioxin in the environment. I and several other scientists have undertaken reviews of the relevant military, historical, and scientific data on exposure to Agent Orange, which will be appearing in the next issues of ESPR (see the overview on p. 146). The papers will analyze the historical facts and environmental data available to assist in determining the potential for soldiers in Vietnam to have absorbed TCDD from Agent Orange. Much of the material to be presented has not been considered in the earlier studies of potential exposure to Agent Orange.

Extensive environmental data on photodegradation and environmental fate of Agent Orange and TCDD were preserved in government technical reports that, though public, were not easily accessible to scientists. Among other things, the data show that in the environmental conditions typical of defoliation operations, a high percentage of any TCDD present in Agent Orange would have been destroyed or biologically inaccessible within a short time after spraying.

Military and historical records from the Vietnam era, many of which were only declassified in recent years, have not previously been taken into account in developing appropriate parameters for studies of exposure to Agent Orange in Vietnam. To take one example, it is not well known that RANCH HAND aircraft frequently received ground fire from enemy forces in the areas being sprayed with herbicides. Fighter escorts were assigned to the missions and returned fire or in many cases suppressed possible resistance with heavy ordinance just in advance of the low-flying unarmed spray planes. A forward air controller directed each mission and was mandated to end it unless all friendly forces in the area were confirmed to be outside the mission target area. This prevented 'friendly fire' casualties from the fighter planes and ordinance. Any persons in the target area at the time of a herbicide mission were likely with hostile forces. Widespread reports of routine spraying of herbicides on friendly forces are simply mistaken and appear to be based on recollections of direct spraying of insecticides (malathion) on troops and military bases to suppress malaria by aircraft similar to those used for herbicide spraying.

The cumulative effect of these and additional records and data to be presented will substantially enhance our appreciation of the 1988 CDC Serum Dioxin Study and even more importantly the understanding of the factors that combined to minimize absorbed doses of dioxin for most veterans. Those veterans found to have elevated serum dioxin levels almost always have a history of handling liquid herbicides. As the CDC Study suggests, neither the soldier one hour and one kilometer away from a mission nor the soldier thirty days and five kilometers away were likely to absorb any significant quantity of TCDD from Agent Orange. Models that construct elaborate indices and predictions on such foundations are assigning accuracy and precision to data that cannot support them.

#### Science and Public Policy

Vietnam and Agent Orange are public policy issues as much as medical and scientific issues – perhaps more so. There are strong public policies favoring our veterans, and rightly so. But our scientific principles ought not favor or disfavor anyone. Sound and accepted principles of verification of exposure models shouldn't be abandoned because they lead us to the conclusion that most Vietnam veterans did not absorb any measurable TCDD from Agent Orange.

As scientists, we cannot ignore the policy context, because in our world today the policies shape the research agenda, and if we are not careful, may affect even the research results. Neither we, nor the IOM Committee should forget that the Committee was created by act of Congress – not to advance our scientific knowledge of TCDD – but to recommend additional diseases to receive Agent Orange benefits in addition to the three diseases Congress designated in the Agent Orange Act.

The extensive medical and scientific studies of Agent Orange over the last thirty-five years tell us that most veterans were not significantly exposed to Agent Orange. They also show that even those with measurable exposure have not suffered ill effects as a result. But we should also acknowledge that many Vietnam veterans do appear to be at risk for a range of diseases and health problems due to the 'Vietnam experience' as a whole [13,14]. Why artificially focus on Agent Orange instead of on providing treatment and benefits for all these veterans?

In hindsight, after all the years of controversy over Agent Orange, perhaps we could have been fairer and more generous to all Vietnam veterans with a program of 'Vietnam experience' benefits rather than Agent Orange benefits. What is really needed is scientific studies of effects of the Vietnam experience on all veterans rather than studies seeking to 'link' more diseases to Agent Orange, which in the present context compromises important scientific principles in the process. It is my hope that the forthcoming articles can contribute significant new data and perspective to the ongoing public dialog on Agent Orange.

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**Overview of Forthcoming Articles on Agent Orange**

**Agent Orange in Vietnam: the Historical Record –**
An evaluation of the military and historical records relevant to possible exposure to Agent Orange in Vietnam

**Environmental Fate and Bioavailability of Agent Orange and Its Associated Dioxin During the Vietnam War –**
An analysis of the fate and bioavailability of Agent Orange and TCDD in the Vietnamese environment

**Exposure to Agent Orange in Vietnam: the Serum-TCDD Evidence –**
A review of studies of TCDD levels in Vietnam veterans and analysis of potential exposure to Agent Orange during the Vietnam War consistent with TCDD levels, historical records, and environmental data

**The Environmental Fate of TCDD in a Spray-Equipment Test Area Receiving Massive Quantities of Agent Orange and Other 2,4,5-T-containing Herbicides –**
A review of the studies on TCDD conducted on Test Area C-52A, Eglin Air Force Base, Florida