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CHAPTER 5

"IN THE FINAL ANALYSIS, THE EVIDENCE OF RISK FROM THE COMPONENTS OF AGENT ORANGE MUST BE OBTAINED FROM THE STUDY OF HUMAN POPULATIONS."

# THE EPIDEMIOLOGY OF AGENT ORANGE AND ITS ASSOCIATED DIOXIN

G. D. LATHROP

This chapter focuses on the realm of adverse human health effects following exposure to Herbicide Orange and TCDD. The many outstanding contributions of toxicologists and pathologists have given a firm platform for clinical concern. Clearly, TCDD is a remarkable, broad-ranged, profound cellular toxin that is, for reasons not fully understood, species specific (35). The key science questions to resolve: is man among the affected species, and, if so, what are the specific measureable attributable symptons, signs, syndromes or diseases? The traditional difficulties in transitioning from the animal laboratory to the human laboratory have been compounded by the progressive array of special interest groups, media representation, legal action, congressional interest, and finally, legislative compensation. Young (36) has aptly described this sequence as the "Crossroads of Science and Social Concern." Now with the legal and compensatory issues largely settled--in the absence of, or because of, the absence of a science answer of causality--the broader questions become: do we have a "cart before the horse" situation, and if so, will the dioxin controversy serve as a model for future solutions of environmental controversies?

Thus, it is appropriate to examine some of the root causes of our slow and, perhaps now, inadequate science.

These fundamental science difficulties fall into the broad categories of methodology, and operational and study circumstance, some of which are listed in Table 1.

Table 1. Fundamental Epidemiologic Difficulties in the Conduct of Health Studies.

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Precedence: Lack of Definitive Acute/Chronic Diseases

Disease Spectrum
- Nonspecificity of Alleged Symptons
- Rareness of Proposed Clinical Endpoints

Limitations of Epidemiologic Methodology
- Case Control vs. Cohort Studies

Study Sample Size
- Population Ascertainment
- Sample Size--Exposure Reversal
- Pitfalls in Merging Cohorts

Exposure to TCDD
- Latency
- Proven vs. Probabilistic
- Vietnam Misperceptions

Assessment of Causal Inferences
- Misclassification
- Bias
- Confounding
  - Use of All Covariates

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These science difficulties in the dioxin controversy are magnified somewhat by the current state of the art and science of the epidemiologic process. Because of the great advances in mathematical statistics in the past decade vis-à-vis the essentially unchanged "artful" data collection techniques in humans and human populations, epidemiology no longer rigidly holds to the computer axiom of "Garbage In--Garbage Out," but may more pose a state of "Garbage In--Elegance Out." The point is that the reviewer scientist should not be mesmerized by the mathematical ingenuity, but must primarily consider the fundamentals of data collection (source, accuracy, etc.) and the study design before accepting a given study as an important piece of work (6).

Further, all studies must be placed into the context of the overall causal inference. As Moore (23) has nicely said in the past, each dioxin study is part of the mosaic needed for an overall scientific conclusion, since each study is not definitive in and of itself. This, of course, largely stems from the facts that the epidemiologic process cannot prove a negative association but can only attempt to bound it by logical inference and that each study generally presents a series of inherent methodologic flaws.

With this background in mind, let me return to the fundamental science difficulties of the dioxin controversy, focusing on the science and operational issues rather than on specific critiques of previous studies.

## ORIGIN OF THE SCIENTIFIC ISSUE

In October, 1969, the first report was made of an increase in congenital abnormalities following administration of 2,4,5-T to pregnant rodents. Because of this report the Department of Defense halted all aerial dissemination of 2,4,5-T containing herbicides in Vietnam during 1970, unfortunately lending

credence to the longstanding enemy propaganda claims of chemical warfare (35). In 1973, the National Academy of Sciences (NAS) conducted an in-depth assessment of the forestry and ecologic implications of herbicide spraying in American-held South Vietnam (24). Health studies were not a planned segment of the evaluation, nor could they be attempted because of the wartime environment. In 1977, Maude DeVictor, a Veterans Administration (VA) claims clerk at the Hines Hospital in Chicago, noted a commonality of subjective complaints in Vietnam veterans (17). Prominent symptons centered about the neuro-asthenia complex, skin disorders, affective disorders, and an increased frequency of birth defects. A non-scientific association was made to Agent Orange exposure in Vietnam and was quickly promulgated by the news media. Initial inquiries to the Department of Defense and the VA induced responses that proper scientific study of U.S. ground personnel would be difficult or inappropriate because of the difficulty in determining true exposure, a point later challenged by a Government Accounting Office (GAO) report (31). In 1979, the first of a series of Swedish case-control studies suggested the additional endpoint of soft tissue sarcoma (5,9,10). From the first involvement of veteran population groups, both scientists and politicians quietly debated whether the Agent Orange controversy had scientific merit, or whether the issue was simply the flagship carrier of veteran concern regarding their postwar treatment by the American public. Also in 1979, the EPA Alsea Oregon study suggested that miscarriages were associated with dioxin exposure, but the study was quickly assailed for methodologic difficulties (30).

From the period of 1980 to the present a great variety of governmental and industry studies were initiated to investigate both specific and generic proposed effects of exposure to dioxin (1,4,7,8,12,16,18,19,20,21,29,32,34,37),

Thus, in relatively short order, the scientific issue transitioned from animal toxicologic studies to social concern to the proving ground of epidemiologic studies.

## STUDY COHORT ISSUES

Several key issues surrounding the study population guide the use of a particular epidemiologic design. They include:

Study Population Size
Determination of the Quality of Exposure
Single vs. Multiple Combined Study Populations
Rareness of the Proposed Clinical Conditions

The relationships of these parameters are depicted in Figure I. Because of uncommon sustained exposure to dioxin, discreet populations available for study are limited. Figure II shows some of the traditional study groups and their crude ranking of exposure relative to each other.

Figure I. Formulation of the Epidemiologic Design.

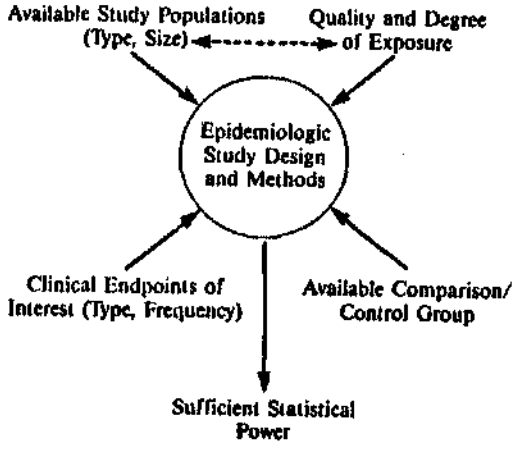
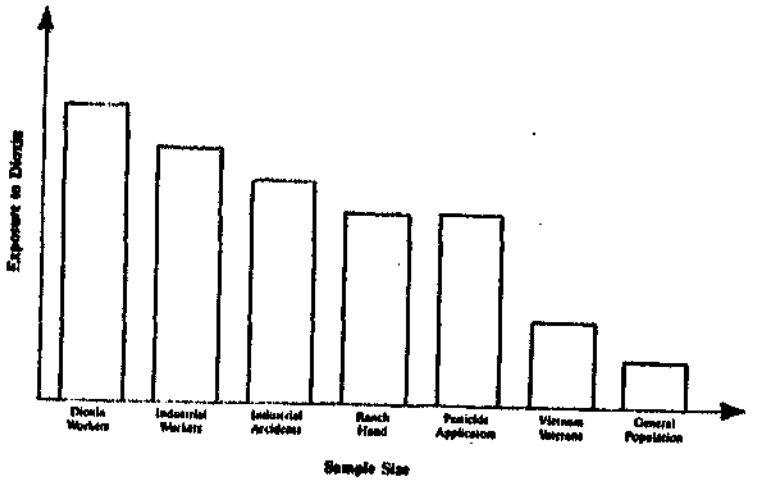


Figure II. The Exposure - Sample Size Quandary.



As a generality, the highest exposed groups represent the smallest population sizes, and conversely, the lower exposed groups contain the highest sample sizes. This exposure-study size reversal is the first fundamental reason why ideal epidemiologic studies cannot be quickly formulated and conducted in the dioxin setting. Several other ramifications of the exposure-sample size reversal are also apparent. Small population groups often present ascertainment and location difficulties, making them more amenable to study bias. If the study focus is upon rare or uncommon diseases, small population groups cannot be justifiably used because of a lack of statistical power. Further, there is great temptation to merge (add) study cohorts as a mechanism of enhancing statistical power. If the cohorts cannot be proven identical with respect to quality and degree of dioxin exposure as well as host parameters (age, sex, race, employment history, etc.) an egregious error of dilution of the effect is likely (22). Stated another way, a small borderline "positive" study might be falsely converted to a negative study with higher stated power and presumably, more scientific credibility. The merging process has, in fact, been proposed by several scientists (12) as a solution to the sample size dilemma; it must be approached with great caution.

The type and frequency of the proposed clinical endpoints under study have a major influence on the overall epidemiologic study design. Table 2 depicts the major signs and symptons of Agent Orange and dioxin exposure both from a literature review up to 1980 and a distillation of the VA's Agent Orange Registry (32).

Table 2. Components of Selected Human Sympton/Signs Following Exposure to Phenoxy Herbicides and/or TCDD.

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## NEURO-PSYCHIATRIC ABNORMALITIES

### ASTHENIA

Anxiety
Depression
Fatigue
Apathy
Loss of Drive
Libido
Impotency
Sleeplessness
Emotional Instability
Anorexia
Dizziness
Learning Disability

### PERIPHERAL NEUROPATHY

Hyporeflexia
Weakness
Paresthesias
Extremity Numbness
Myalgia
Gait Disturbance
"Mild" Paresis

## DERMATOLOGIC DISEASES

Chloracne
Porphyria Cutanea Tarda
Hyperpigmentation
Hirsutism (Body)
Alopecia of the Scalp

## OTHER DISORDERS

### HEPATIC DYSFUNCTION

Cholesterol
SGOT, SGPT, LDH

### RENAL DYSFUNCTION

Proteinuria
Decreased Output
Tubular Degeneration
Glomerular Degeneration
Renal Glucosuria

### GI DISTURBANCE

Nausea
Vomiting
Diarrhea
Gastritis
ABD Pain
Flatulence

### CARDIAC DISTURBANCE

Bradycardia
Tachycardia
Atrial Fibrillation

From the perspective of the causal relationship, some scientists have interpreted the wide array of signs and symptoms as highly supportive of the animal studies and of the notion that dioxin indeed induces multi-organ system effects. Other scientists view the sympton complex as indicative of alternant etiologies, including chance, bias, and social causes. In formulating a suitable epidemiologic study, the above broad based symptom complex poses formidable design issues. Most of the alleged symptons are highly subjective in nature and require sophisticated and detailed survey research (questionnaire) methods or laboratory testing for validation. The reported clinical signs are generally transitory following acute exposure and thus could not be relied upon validly for cross-sectional or follow-up studies. In addition, only the sign of chloracne could be considered (and not strictly so) as specific for dioxin exposure, while the rest are relegated to nonspecific signs and symptoms (3). Wide clinical nets must be cast to determine if attributable disease syndromes or diseases exist. In the other extreme are the proposed rare disease endpoints of soft tissue sarcoma and porphyria cutanea tarda. Clearly, the rareness of these diseases precludes any active clinical attempt to describe them by cross-sectional or prospective cohort designs. Thus, the second fundamental cause of the dioxin complexity is the extreme divergence between the alleged disease conditions (common subjective vs. rare objective) with little middle ground available for powerful classic studies using multiple independent designs.

The third fundamental reason for the science complexity centers upon the true exposure circumstance of the study population. Since chloracne is the herald sign of dioxin exposure, some scientists believe that chloracne is a requirement as a precursor to the emergence of serious disease (28). The epidemiologic viewpoint of this notion is somewhat contrary

and holds that chloracne is not a required precursor but is merely a point on the overall spectrum of illness. Further, it is likely that the study of chloracne populations is simply a focused study upon the higher exposed segment of the population, a process that is a traditional starting point in occupational epidemiology (13,14,25). With respect to the study populations of industrial workers, dioxin workers, pesticide applicators, and the Air Force Operation Ranch Hand members, the exposure question is generally not "if," but "how much?" Exposure estimation has magnetic appeal to the scientist because a demonstrated positive dose-response relationship is one of the most convincing of the eight parameters used in establishing a cause-and-effect relationship. For the above population groups, a variety of exposure estimators are feasible: industrial hygiene data and time-weighted projections; occupational titles adjusted by person-years of employment; an average time-weighted experience in dispensing herbicides. For industrial accident populations, exposure indices derived from soil contamination levels or concentric circle analyses are reasonable approaches.

However, for most Vietnam veterans and certainly the general United States population, the exposure question is "Did it occur, yes or no?" not "how much?" For these populations assignment of exposure is subject to overwhelming possible bias or misclassification (15). More on this later for the Vietnam veterans. Unfortunately, in epidemiology, most exposure estimators do not pan out. Linear relationships between the exposure estimator and the expected effects are rare because of the variability in these measurements plus such intervening factors as age, sex, race, and susceptibility.

Thus, the three fundamental difficulties of sample size-exposure reversal, ascertainment of exposure, and the breadth of alleged symptoms and disease are intertwined to produce a

science polemic of the first order. Since the ultimate resolution depends upon the strengths and weaknesses of the scientific methodology, a brief description of the available epidemiologic designs is in order.

## LIMITATIONS OF EPIDEMIOLOGIC METHODOLOGY

A hierarchal order of scientific sophistication is suggested by the type of study undertaken, and further implies a relative contribution to the solution of an issue. This ranking is displayed in Table 3.

A notable exception to this ordering is the substantial worth of well described case reports and case series to exposure-disease problems. Such efforts by toxicologists, clinicians and pathologists are invaluable in defining acute disease and are often instrumental in predicting chronic effects. Similarly, uncontrolled mortality or morbidity studies may provide useful clues that merit inclusion in larger controlled studies. Multiple design parameters can be enfolded into most of the listed types of studies and can be as convoluted and complex as the circumstance and available funding allow. For example, one Government study uses a nonconcurrent prospective design with a mortality component and four referent groups, a retrospective morbidity assessment, a cross-sectional morbidity study, a 20-year follow-up study, all with both matched pair and stratified analytic techniques; additionally, this study possesses the opportunity of conducting embedded case-control cancer studies and specialized comprehensive fertility/reproductive efforts (19). Most epidemiologic studies in the dioxin arena, however, are less interlinked and generally condensed to either case-control studies or cohort studies. The advantages and disadvantages of these approaches are summarized in Table 4.

Table 3. Science Assessment of Medical Studies.

| Study Parameters (Design) | Type of Study | Conditions of Study |
|---|---|---|
| | Case Report | |
| | Case Series | |
| | Literature Reviews | |
| Concurrent<br>Nonconcurrent<br>Cross-Sectional<br>Retrospective<br>Prospective<br>Matched<br>Randomized<br>Stratified | Mortality Studies | Uncontrolled, Controlled<br>Death Certificate vs.<br>Medical Record Confirmation |
| | Morbidity Studies | Uncontrolled, Controlled |
| | Follow-up Studies | Uncontrolled, Controlled |
| | Experimental Studies | Natural, Planned |

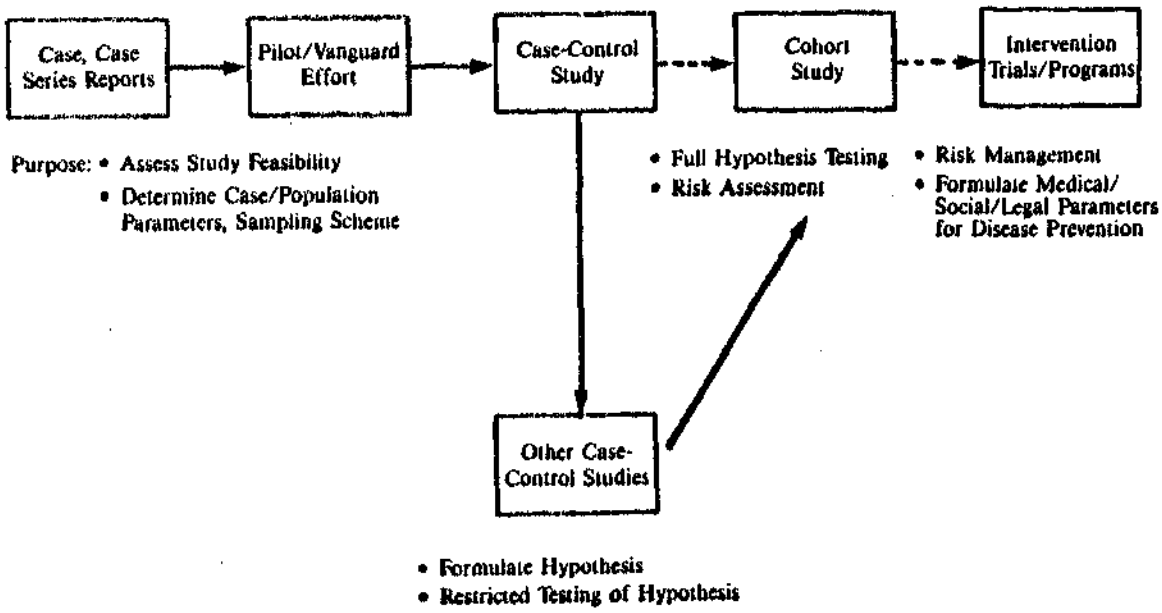
Table 4. Advantages and Disadvantages of the Conduct of Case-Control and Cohort Epidemiologic Studies.

| Case-Control Study | Cohort Study |
|---|---|
| Advantages: | |
| Fast, Inexpensive | Accurate Estimates of Risk |
| Tailormade for Rare Diseases | Biases Amenable to Control |
| Easily Repeatable if Causal Association Truly Present | |
| Disadvantages: | |
| Highly Subject to Bias | Laborious, Time-consuming |
| Often Difficult to Assess the True Risk | Expensive |
| | Cannot Practically Investigate Rare Diseases |
| | Difficult to Apply to Diseases of Long Latency |

As a brief review, the case-control study begins with a collection of disease cases which are then assigned proper controls; both the cases and the controls are then retrospectively assessed for the presence or absence of the exposure or causative variable. This method is the day-to-day workhorse used in epidemiology, and many articles and texts have highlighted its applications and limitations. The case-control method is quick, inexpensive, ideal for rare diseases, generally repeatable, and often the only available technique that avoids ethical barriers. Alternatively, this method is terribly subject to bias, and in particular, respondent bias when the exposure assignment is made. Most of the published dioxin studies have used this method in one form or another, and significant caution is required in the interpretation of results. In contrast to the case-exposure sequence of case-control studies, cohort studies begin with exposed individuals and a determined control or comparison group consisting of non-exposed individuals; the entire cohort is then observed forward in time from the point or points of exposure, and disease conditions of interest are recorded. Because of the extreme cost and the complexity of the data base, cohort studies usually require government or industry support. The advantages and disadvantages of the cohort method are almost a point by point opposite of the case control technique.

The key feature is that for exposure scenarios like Agent Orange and dioxin where there has been substantial media coverage, respondent bias to the exposure circumstance may well exceed the correction capacity of a cohort study. Overall, because of the relative shortcomings of each epidemiologic method, a series of studies using different methods and designs are required to establish a causal relationship firmly. A traditional study sequence is depicted in Figure III.

Figure III. Traditional Epidemiologic Study Sequence.




General emphasis points are: 1) pilot or vanguard efforts are often not desirable when the exposed study population size is small so as to avoid "contamination" and eventual loss of additional size to the full study, 2) initial case-control studies are best used for hypothesis testing, and 3) causal relationships are more accurately determined with the addition of cohort studies.

With the limitations of the epidemiologic process in mind and recalling the three fundamental components of the science knot, it is now appropriate to assess the credence of the links of specific diseases to exposure to Agent Orange and dioxin.

CHLORACNE:

Numerous clinical and epidemiologic studies have unequivocally established the causal link between chloracne and exposure to dioxin (13,14,25). There is no scientific debate to this fact. However, chloracne is not specific to dioxin exposure and may be induced by other compounds including the dibenzofurans (34). The diagnosis is easily made in the acute fulminate stage but may be exceptionally difficult in its chronic form, often necessitating biopsy confirmation or the examination by a dermatologist particularly astute with chloracne. The disease may be diagnosed 30 years after onset in some cases (28). The only difficulty presented by chloracne is the differential diagnosis with adolescent acne in population groups with low exposure. In such instances, as with Vietnam veterans, the diagnosis must be attempted by detailed questionnaire techniques, clinical examination with biopsy, or by medical record review. This approach may be confounded by respondent bias as well as by a lack of contemporary clinical acumen. As mentioned previously, it may well be that confirmed chloracne within the study population may merely represent a level of dioxin exposure that merits further study for the emergence of other clinical conditions.

PROPHYRIA CUTANEA TARDA:

Porphyria cutanea tarda (PCT) is the most common form of a rare class of diseases (porphyrias) affecting hemoglobin metabolism. The porphyrias range in severity from life threatening hepto-dermatologic disease to subclinical illness. Their classification and etiologies are complex. PCT may be caused by hereditary factors, chronic alcoholism, exposure to diverse chemicals, or combinations thereof. The causal association of PCT and dioxin was made following two independent industrial episodes in New Jersey and Czechoslovakia. Chloracne was also a predominent sympton in both plants where pentachlorophenol was produced. However, pure exposure to TCDD was far from

shown, and in retrospect, it is possible that confounding exposures, particularly to the chlorinated benzenes, may be implicated in the induction of the PCT cases (11). Thus, definitive evidence of the role of TCDD must await additional industrial circumstances or possibly the conduct of case-control studies. However, because of the known etiologic role of other chemicals, the extreme rareness of PCT, and the difficulty of respondent bias, it is unlikely that case-control efforts would generate clear-cut results to the satisfaction of the scientific community unless an international comprehensive registry or data base is formulated.

SOFT TISSUE SARCOMA:

Soft tissue sarcoma (STS) is a generic malignant cancer that actually embodies 110 distinct histologic subtypes found in essentially all anatomic locations. The histologic differential diagnosis between sarcoma and carcinoma is often difficult,and the variation between pathologists often leads to substantial misclassification of the tumor. For this reason, and as well demonstrated by Fingerhut et al. (8), histologic confirmation by an expert or expert panel is a requirement to conduct a meaningful study of STS. The quick approach of a case-control study using a death certificate data base also presents the unusual problem of very significant underascertainment of the sarcomas. Because of a quirk in the medical coding system, up to 40 percent of the fatal deep-seated sarcomas may be missed (8).

Due to the extreme rarity of STS, as exemplified by a United States death rate of 0.07 percent, only the case-control method stands a reasonable chance to clarify the causal association. The technique of merging industrial cohorts from mortality studies or surveillance programs may also be acceptable and provide useful data in the presence of marked case clustering, provided that the previously mentioned merging cautions are observed and that measurement of the cancer patterns follows the merging process. While these techniques

may or may not be ultimately useful, the basic question of biologic plausibility remains. According to some pathologists, it is difficult to imagine how a single chemical could induce multiply related cancers in a diversity of anatomic sites. Such a phenomenon, if true, would run contrary to the classic cancer-chemical models which now exist (e.g., mesothelioma and asbestos; and polyvinyl chloride and brain tumors).

The association of STS and dioxin exposure was raised by four Swedish reports beginning in 1979 (5,9,10). These serial papers reveal slightly different study and referent groups to obtain a "relative risk" of 5-6, impressive, to say the least. However, all these studies used the case-control method, and serious questions are posed for the issue of respondent or proxy respondent bias. In the view of some workers, the methodologic weaknesses of the Swedish studies render the association of STS and dioxin to the lowest order. However, the association is fixed in the minds of many, including Congress, and clearly, all dioxin scientists will have to account for STS if their study population and epidemiologic design permit.

Thus, because of STS diagnostic difficulties, under-ascertainment induced by the International Classification of Disease (ICD-9) coding, and disease rareness which mandates a case-control design, many more carefully conducted studies will be required to resolve the suspected STS-dioxin association.

FERTILITY/REPRODUCTIVE ABNORMALITIES:

Fertility difficulties, fetal wastage, and overt birth defects were alleged by Vietnam veterans to be caused by exposure to Agent Orange. In terms of biologic plausibility, there is no known human example or animal model to demonstrate that male exposure alone can induce such effects. Four recent

epidemiologic studies have shown mixed results with respect to these endpoints. The Dow Chemical Company study of workers exposed to chlorophenols and dioxin largely showed negative findings (29). For the parameters it attempted to cover, it was a credible effort. The Center for Disease Control (CDC) study of veterans and Vietnam veterans in the Atlanta, Georgia, area also largely revealed negative results, but it should be noted that certain analytic procedures and statistical assumptions merit additional review (4). The Australian birth defects study, using a classic case-control design, showed that a Vietnam veteran was at no higher risk of fathering a defective child than a non-Vietnam veteran (1). The Air Force Ranch Hand study, using a nonconcurrent prospective design with a physical examination component, determined negative findings for most classic fertility/infertility indices, severe and moderate birth defects, and both total sperm counts and percent abnormal sperm (19). However, in this latter study, for limited birth defects (e.g., birth marks and skin tags), neonatal deaths, and physical handicaps, the exposed group showed statistically significant excesses. All findings were based upon subjective questionnaire data, unverified by birth certificate or medical record reviews. An overreporting bias was suggested in the data set, but it was not fully analyzed. These baseline findings are the subject of current intensive record verification and follow-up; the findings should be published in late 1986.

Thus, with respect to fertility/reproductive abnormalities, the preponderance of evidence is largely to the no-effect side, but additional studies and follow-up are still indicated. It is anticipated that the current CDC morbidity study being conducted at the Lovelace Clinic and the first follow-up Ranch Hand study at the Scripps Clinic will provide significant clarifying data.

OTHER FINDINGS:

The Air Force Ranch Hand study noted the curious finding of peripheral pulse deficits in the exposed group. There is no known mechanism to explain this effect (19). Of considerable interest was a similar but statistically nonsignificant finding in the Times Beach morbidity study (7).

The unpublished work of Ward has stimulated considerable interest in the possible adverse effects of dioxin on the immune system (33). The Ranch Hand baseline study showed no group differences with respect to B & T cell count and functional tests but did reveal for the first time the profound effects of age and smoking upon these measurements (19). Additional assessments of these immune parameters are being conducted in the Ranch Hand follow-up study as well as the CDC morbidity study.

The discussion to this point has made several references to the possible exposure differences to Agent Orange in veteran cohorts. Because this fundamental point will have great bearing on the interpretation of future veteran study results, a review of the exposure dilemma is in order.

## THE EXPOSURE CONTROVERSY FOR VIETNAM VETERAN COHORTS

DIRECT EXPOSURE:

Since 1978, Vietnam veterans have alleged that they received substantial direct exposure to Agent Orange via aerial dissemination (OPERATION RANCH HAND). Media "documentaries" (best exemplified by Mr. Kurtis' Vietnam's Deadly Fog [17] ), statements to the media by veterans and veteran activist groups, and widely publicized Congressional hearings have presented a convincing scenario of significant direct exposure, to the point, in fact, where the public and most scientists believe that military service in Vietnam is equivalent to Agent Orange exposure.

Because this misperception will have profound effects in the interpretation of ongoing or future studies, it is important to balance the record. I believe that the following statements accurately reflect the exposure circumstance in Vietnam:

1. U.S. ground personnel were only rarely directly exposed to aerially dispersed Agent Orange because of the related facts that:

   a. The Air Force fixed-wing aerial herbicide missions were flown 4-6 weeks in advance of anticipated ground conflict (e.g., remote areas generally away from U.S. troop concentrations [2,3,5] ).

   b. Army commanders were included in the approval cycle for all missions to improve mission effectiveness and to restrict U.S. troop entry because of the often intense fire cover provided by U.S. fighter escorts.

2. Some U.S. ground personnel were undoubtedly exposed to Agent Orange via helicopter and backpacks used to spray camp perimeters. On extremely rare occasions, a few soldiers may have been exposed to Ranch Hand aircraft in the process of experiencing emergency dumps of herbicide. Many personnel may have been exposed to contaminated soil, dust, water, and foodstuffs, but the occurrence, extent, or relevance of such exposure is unknown. The U.S. personnel who occasionally assisted in herbicide loading operations were likely exposed. Because of limitations in military records, precise identification of any of the above persons is virtually impossible.

3. U.S. Air Force Ranch Hand personnel: pilots, navigators, crew chiefs, and aircraft repairmen were substantially

exposed to Agent Orange and many other herbicides while in Vietnam. It is crudely estimated that the average annual exposure of an aircrew member was 1,000 times the dose received by an unclothed man standing directly beneath a low-flying spraying aircraft (19). Precise quantitation of the exposure of a Ranch Hand member is not possible, nor can relative exposure be determined between occupational categories.

4. Most U.S. servicemen in Vietnam were intentionally exposed to aerially disseminated malathion in an effort to quell the malaria problem. The malathion was dispensed by virtually the same fixed-wing aircraft that sprayed Agent Orange (2). It is understandable why many veterans honestly believe that they were sprayed by these aircraft in Vietnam; they were. This fact precludes questionnaire techniques to determine exposure because of misclassification of the responsible aircraft.

5. Because of a lack of chloracne in Ranch Hand personnel and U.S. Army personnel, it is inferred that these populations received substantially less exposure than industrial populations (19).

PROBABILISTIC EXPOSURE:

Following the Congressional mandate to conduct an epidemiologic study of U.S. ground personnel, significant scientific energy was devoted to the clarification of the exposure issue. The second GAO report on the Agent Orange issue suggested the use of the HERBS tapes, a computerized chronicle of the map coordinates of "spray on" and "spray off" points for each herbicide mission (31). By calculating a time-distance matrix of the soldier's headquarters location to the spray line, a "likelihood exposure index" could be constructed for each study and comparison subject, or alternatively,

the index could be used to determine the study and comparison populations. This notion has transitioned in design through the UCLA School of Public Health, the Department of Defense, to the current Stellman and Stellman approach of a concentric circle analysis (27). While I believe that these efforts have been commendable and represent a valiant attempt, I think they will eventually be shown to be without scientific merit for several reasons:

1. True direct exposure in Vietnam was a dichotomous event, not a probabilistic event.

2. Application of any probabilistic approach is made <u>without</u> knowledge of the true misclassification rates of:

   a. Designating an exposed person as unexposed and,
   b. Designating an unexposed person as exposed.

   Determination of these errors is not possible. It is therefore not possible to calculate an overall required study size to discern true specified group differences (exposed, unexposed) at standardized alpha and 1-Beta levels. Stated another way, such a study could not validly assure the scientific community that it had the ability to detect the putative effect at a given frequency at a stated study size.

3. The map coordinates cited in the HERBS tapes are largely accurate, but many are inaccurate and based only on the guesstimates of Ranch Hand pilots and navigators who were under extreme combat or terrain-flying stress. Straight line approximations or multi-leg zig-zag patterns can only be viewed as gross approximations of many of the missions in Vietnam. This error source can only be adequately factored into the probabilistic approach by the use of additional crude assumptions.

4. The proximity of a given individual to an actual spray mission the moment it was flown as determined by a review of Army battalion or company personnel records represents a clear overreaching of the data source. Errors implicit in such crude approximations are incalculable.

The ultimate distillation of the probabilistic model(s) is that it probably measures true direct exposure with the same precision as a coin-flip. If it can do better, it is the responsibility of the investigators to prove that point, and in a clear and convincing way. Further, in the discussions or writings of probabilistic methods, there is a noted tendency to quickly drop the proper caveats of "probable, likely, likelihood," etc., when discussing exposure, often leading both scientists and lay readers into the unwarranted shorthand assumption of true exposure.

The problems associated with specifying the true Vietnam exposure scenarios and the likely interpretative problems that will arise from veteran studies should renew scientific efforts to explore further study opportunities in industrial or industrial accident populations.

## AN OUTLOOK FOR DIOXIN EPIDEMIOLOGY

The next five years will bring forth a variety of dioxin/Agent Orange studies, predominantly of the case-control design. Those cohort studies focusing on Vietnam veteran populations will likely be well conducted, elegant, expensive, and considerably nagged by the exposure issue and interpretive considerations.

The novelty of well conducted and large fat biopsy studies should emerge, stimulating new discussions on the dioxin half-life, mass spectroscopy, and the relevance of

Vietnam exposure (37). As the causal relationship between chloracne and dioxin is well established, few additional studies should be published. Because of the confounding effects of multiple industrial chemical exposures, chronic alcoholism, and genetic contributions, plus the extreme rarity of porphyria cutanea tarda, a cause-and-effect relationship with dioxin will not be made unless registry-based international collaborative studies are conducted. The prospect for consensus determinations on soft tissue sarcoma, other cancers, excess generic mortality, fertility/reproductive abnormalities, neuroasthenia, psychological disturbances, etc., is far more favorable than for PCT. However, the entire resolution process will continue to be slow and difficult, unfortunately lending further justification to the social/legal solution of an issue that heretofore resided in the scientific domain.

REFERENCES


1. Australian Veterans Health Studies, 1983. Case-Control Study of Congenital Anomalies and Vietnam Service (Birth Defects Study). Report to the Ministry for Veterans' Affairs, January, 1983. Australian Government Publishing Services, Canberra. 127 pp.

2. Buckingham, W.A., Jr., 1982. Operation RANCH HAND. The Air Force and Herbicides in Southeast Asia, 1961-1971. Office of Air Force History, United States Air Force, Washington, D.C. 253 pp.

3. Crow, K.D., 1981. Chloracne and its Potential Clinical Implications. Clin. Exp. Dermatol. 6 (3):243-257.

4. Erickson, J.D., Mulinare, J., McClain, P.W., et al., 1984. Vietnam Veterans' Risks for Fathering Babies with Birth Defects. J. Am. Medical Assoc. 252:903-912.

5. Erickson, M., Hardell, L., Berg, N.O., Moller, T., Axelson, O., 1981. Soft-Tissue Sarcomas and Exposure to Chemical Substances: A Case-Referent Study. Br. J. Ind. Med. 38:27-33.

6. Diamond, G.A., and Forrester, J.S., 1983. Clinical Trials and Statistical Verdicts: Probable Grounds for Appeal. Ann. Internal Med. 98:385-394.

7. Falk, H., Stehr, P.A., Stein, G.F., Sampson, E.J., Donnell, H.D., Schramm, W.F., Webb, K., Gedney, W.B. A Pilot Epidemiologic Study of Health Effects Due to 2,3,7,8-Tetrachlorodibenzo Dioxin (TCDD) Contamination in Missouri. Danbury Report 18: Biological Mechanisms of Dioxin Action; Cold Springs Harbor Laboratory, pp. 447-460, 1984.

8. Fingerhut, M.A., Halperin, W.E., Honchar, P.A., Smith,A.B., Groth, D.H., and Russell, W.O. An Evaluation of Reports of Dioxin Exposure and Soft Tissue Sarcoma Pathology in U.S. Chemical Workers. Danbury Report 18: Biological Mechanisms of Dioxin Action; Cold Springs Harbor Laboratory, pp. 461-470, 1984.

9. Hardell, L., and Sandstrom, A., 1979. Case-Control Study: Soft-tissue Sarcomas and Exposure to Phenoxyacetic Acids or Chlorophenols. Br. J. Cancer. 39:711-717.

10. Hardell, L., 1981. Relation of Soft Tissue Sarcoma, Malignant Lymphoma and Colon Cancer to Phenoxy Acids, Chlorophenols and Other Agents. Scand. J. Work Environ. Health. 7:119-130.

11. Hobson, L.B., April, 1983. Unpublished Report: Porphyria Cutanea Tarda. Agent Orange Projects Office, Veterans Administration, Washington, D.C.

12. Honchar, P.A., and Halperin, W.E., 1981. 2,4,5-T, Trichlorophenol, and Soft Tissue Sarcoma. Lancet, Jan.31: 268-269.

13. Jirasek, L., Kalensky, J., Kubec, K., 1973. Acne Chlorina and Porphyria Cutanea Tarda during the Manufacture of Herbicides. Cesk. Dermatol. 48(5):306-315.

14. Jirasek, L., Kalensky, J., Kubec, K., Pazderova, J., and Lukas, E., 1974. Acne Chlorina, Porphyria Cutanea Tarda and Other Manifestations of General Intoxication during the Manufacture of Herbicides. II. Cesk. Dermatol. 49 (3):145-157.

15. Kleinbaum, D.G., Morgenstern, H., and Kupper, L.L., 1981. Selection Bias in Epidemiologic Studies. Am. J. Epidemiol. 113(4):452-463.

16. Kogan, M.D., and Clapp, R.W. Mortality among Vietnam Veterans in Massachusetts, 1972-1983. Massachusetts Office of Commissioner of Veterans Services, Agent Orange Program: Massachusetts Department of Public Health, Division of Health Statistics and Research, January 18, 1985.

17. Kurtis, B., 1978. "Agent Orange: Vietnam's Deadly Fog." Transcript of a television documentary aired March 12, 1978, WBBM-TV, Chicago, Ill. 30 pp.

18. Lathrop, G.D., Moynahan, P.M., Albanese, R.A., and Wolfe, W.H. An Epidemiologic Investigation of H-alth Effects in Air Force Personnel Following Exposure to Herbicides: Baseline Mortality Study Results. Annual Report (Initial), United States Air Force School of Aerospace Medicine, June 30, 1983.

19. Lathrop, G.D., Wolfe, W.H., Albanese, R.A., and Moynahan, P.M. An Epidemiologic Investigation of Health Effects in Air Force Personnel Following Exposure to Herbicides: Baseline Morbidity Study Results. United States Air Force School of Aerospace Medicine, February 24, 1984.

20. Lamb, J.C., Moore, J.A., and Marks, T.A., Evaluation of 2,4-dichlorophenoxyacetic acid (2,4-D), 2,4,5-trichlorophenoxy-acetic acid (2,4,5-T), and 2,3,7,8-tetrachlorobidenzo-p-dioxin (TCDD) Toxicity in C57BL/6 Mice: Reproduction and Fertility in Trated Male Mice and Evaluation of Congenital Malformations in their Offspring. National Toxicology Program, Research Triangle Institute, Research Triangle Park, N.C. Report No. NTP-80-44. 57 pp.

21. Lawrence, C.E., Reilly, A.A., Quickenton, P., Greenwald, P., Page, W.F., and Kuntz, A.J., 1985. Mortality Patterns of New York State Vietnam Veterans. Am. J. Public Health, 75:277-279.

22. Marshall, J.R., Priore, R., Graham, S., and Brasure, J., 1981. On the Distortion of Risk Estimates in Multiple Exposure Level Case-Control Studies. Am. J. Epidemiol. 113(4):464-480.

23. Moore, J.A., 1980. Report of the Agent Orange Working Group Science Panel. Department of Health and Human Services, Washington, D.C.

24. National Research Council, 1974. The Effects of Herbicides in South Vietnam: Part A. Summary and Conclusions. National Academy of Sciences, Washington, D.C. AD-774-749.

25. Reggiani, G., 1979. Estimation of the TCDD Toxic Potential in the Light of the Seveso Accident. Arch. Toxicol. 2:291-302.

26. Smith, A.H., Pearce, N.E., Fisher, D.O., Giles, H.J., Teague, C.A., and Howard, J.K., 1984. Soft Tissue Sarcoma and Exposure to Phenoxyherbicides and Chlorophenols in New Zealand. JNCL. 73:111-117.

27. Stellman, J.M., and Stellman, S.D. Issues, Options and Methodologies in the Determination of Exposure to Phenoxy-Herbicides among Vietnam Veterans. Written Testimony Presented to the United States District Court, Eastern District of New York, February 20, 1985.

28. Suskind, R.R., and Hertzberg, V.S., 1984. Human Health Effects of 2,4,5-T and Its Toxic Contaminants. JAMA. 251:2372-2380.

29. Townsend, J.C., Bodner, K.M., Van Peenen, P.F., Olsen, R.D., and Cook, R.R., 1982. Survey of Reproductive Events of Wives of Employees Exposed to Chlorinated Dioxins. Am. J. Epidemiol. 115:695-713.

30. U.S. EPA, 1979. Report of Assessment of a Field Investigation of Six-Year Spontaneous Abortion Rates in Three Oregon Areas in Relation to Forest 2,4,5-T Spray Practice. OTA/EPA.

31. U.S. General Accounting Office (USGAO), 1982. VA's Agent Orange Examination Program: Actions Needed to More Effectively Address Veterans' Health Concerns. GAO/HRD-83-6, October 25. 78 pp.

32. Veterans Administration, Department of Medicine and Surgery. Review of Literature on Herbicides, Including Phenoxy Herbicides and Associated Dioxins. Volume I. JRB Associates: 1981.

33. Ward, A.M., 1978. Investigations of the Immune Capability of Workers Previously Exposed to 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD). Unpublished. Department of Immunology, Hallamshire Hospital, Sheffield, U.K. 9 pp.

34. Wolfe, W.H., and Lathrop, G.D., 1983. A Medical Surveillance Program for Scientists Exposed to Dioxins and Furans. Environ. Sci. Res. 26:707-716.

35. Young, A.L., Calcagni, J.A., Thalken, C.E., and Tremblay, J.W., 1978. The Toxicology, Environmental Fate, and Human Risk of Herbicide Orange and its Associated Dioxin. USAF Occupational and Environmental Health Laboratory Technical Report No. USAF OEHLTR 78-92, 262 pp.

36. Young, A.L., 1981. Agent Orange at the Crossroads of Science and Social Concern. Report Number 2750-81, Air Command and Staff College, Air University, Maxwell AFB, AL 36112. 63 pp.

37. Young, A.L., Kang, H.K., Shepard, B.M., 1985. Chapter 13, Rationale and Description of the Federally Sponsored Epidemiologic Research in the United States on the Phenoxy Herbicides and Chlorinated Dioxin Contaminants. Keith, L.H., Rappe, C., and Choudhary, G. (Editors). Chlorinated Dioxins and Dibenzofurans in the Total Environment II. Butterworth Publishers, Stoneham, Mass., 02180. 155-166.