

CHAPTER 4

PHYSICAL EXAMINATION METHODOLOGY

The 1987 followup examination was provided to all eligible participants who were invited, scheduled, and traveled to the examination site in La Jolla, California. The individuals invited included (1) those who had been invited to the Baseline and/or 1985 followup studies and attended one or both studies, those who chose not to participate, those who completed the Baseline questionnaire only, or those who were unlocatable in 1982 and/or 1985 and (2) Comparisons who had not been invited previously, but who were selected as replacements for noncompliant Comparisons in the 1987 followup. As noted in the Baseline Report, all potential study participants were verified as eligible for the Air Force Health Study (AFHS) following a detailed review of military personnel records. Replacement individuals were selected, by matching data on the self-perception of health from the noncompliant Comparison (obtained from the 1985 telephone survey) with those of the replacement candidate (see Chapter 3 for details).

The followup examination consisted of the following major elements:

- Review-of-Systems Questionnaire
- Psychological Testing
- Physical Examination
- Laboratory Testing
- Specialized Testing, e.g., Phlebotomy for Measurement of Serum Dioxin
- Psychological and Medical Outbriefings.

The Combat Experience Questionnaire and skin, hair, and eye color determinations, which were components of the 1985 followup examination, were conducted for all participants who did not attend the 1985 followup.

Details of the above examination elements were carefully prescribed by the Air Force and set forth as contractual requirements. Clinical variations were neither desired nor authorized; all proposed examination procedural changes were reviewed in detail by Air Force technical and contractual personnel prior to the start of the examinations. An important objective of the technical review was to ensure that bias was not created by any procedural change. The requirement to maintain blind examinations was particularly stringent: The clinical staff was prohibited from knowing or seeking information as to the group identity (Ranch Hand, Comparison) of any participant. At the end of the examination, each participant was asked to note on the critique form whether such information was sought by any member of the clinical or paramedical staff. A total of five participants indicated that an examining physician asked about specific duties in Southeast Asia (SEA); all of these were within the first few weeks of the 1987 followup. Following these occurrences, the critique form was modified to request that the onsite monitor be contacted if any inquiry about specific duties in SEA was made.

As discussed in the 1985 followup report, in mid-1986, strong correlations between dioxin levels in fat tissue and serum were demonstrated by the Centers for Disease Control (CDC) and other institutions. Because of these

results, the Air Force engaged in a collaborative study with CDC to determine the serum dioxin levels of the participants of the AFHS. Of the 2,008 volunteers, blood was successfully drawn from 1,999 participants for this purpose. Due to the time required to analyze the samples, the measurements of serum dioxin levels were not available for analysis and inclusion in this report. These data will be analyzed and reported separately.

EXAMINATION CONTENT

Examination content, as designed by the Air Force, emphasized detection of medical endpoints suspected of being associated with exposure to phenoxy herbicides, chlorophenols, or dioxin. In 1985, findings of the Baseline examination were used by the Air Force to direct changes in the 1985 followup examination. Since the 1987 followup examination was initiated prior to the full analysis of the data from the 1985 examination, most modifications to the examination format and procedures were founded upon quality control issues and the desire to make the clinical content of the examination more responsive to the medical needs of the participants. The general content of the physical examination and psychological test battery is shown in Table 4-1, and the complete laboratory test series is displayed in Table 4-2.

As in the Baseline and 1985 studies, quality control requirements for both laboratory testing and clinical procedures were extensive. Although details are provided in Chapter 6, the following categories provide an overview of the extent of the quality emphasis. For laboratory testing, single reagent lots and control standards were used when practical, duplicate specimens were routinely and blindly retested, testing overlaps were mandatory when test reagents required change, and fast initial response cumulative sum were used to detect rapidly any subtle test drift over time. In addition, 50 specimens from the Baseline serum bank were retested to assess the comparability of laboratory methods. The Scripps Clinic and Research Foundation (SCRF) clinical team was carefully instructed to assure clinical quality. The quality control elements included: a pretest of the examination process; detailed clinical inspection techniques by SCRF, Science Applications International Corporation (SAIC), and Air Force physicians and personnel; preprinted mark-sense examination forms; clinical quality assurance meetings to detect and correct problems; and blindness of exposure status at the examination.

Based on the 1985 followup, clinical quality control enhancements were made to improve measurement techniques in the 1987 followup. The digit preference noted in systolic and diastolic blood pressure readings in the 1985 followup led to the use of automated blood pressure recording; all other parameters of the blood pressure readings (e.g., sitting position, three recordings, nondominant arm at heart level) were not changed. The problem in skin test reading encountered in the 1985 followup was met by a rigorous quality control plan that included the following elements: refresher training for readers; a reading of the four skin tests of all participants by both readers, each blind to the results of the other; a reread of 10 percent of all tests by each of the readers, each blind to the previous reading, and a weekly report citing numbers and proportions of participants with possible allergy, reversal of induration-erythema measurements, and untoward skin reactions or other reading problems (e.g., participant refusal). In addition, new skin

TABLE 4-1.**Elements of the 1987 Followup Physical Examination**

Elements	Remarks
General Physical Examination	Internist
Neurological Examination	Neurologist
Dermatologic Examination	Dermatologist
Electrocardiogram	Resting, 4-Hour Fasting and Nicotine Abstinence
Chest X Ray	Radiologist
Immunologic Studies	40% Random Sample
Skin Test Studies	80% Sample
Psychological Evaluation: Millon Clinical Multiaxial Inventory (MCMI) Symptom Checklist 90-R (SCL-90-R)	
Pulmonary Function	Internist with Subspecialty in Pulmonary Disease
Audiometry Examination	Audiologist
Vision Screening and Tonometry	Technician
Patient Outbriefing and Discussion of Individual Results	Medical Diagnostician, Internist, and Ph.D. Psychologist

TABLE 4-2.

Laboratory Test Procedures of the 1987 Followup Physical Examination

Clinical Laboratory

Fasting Glucose	2-Hour Postprandial Glucose
Blood Urea Nitrogen (BUN)	Creatine Phosphokinase (CPK)
Cholesterol	Total Bilirubin
HDL Cholesterol	Direct Bilirubin
Triglyceride	Total Protein
Aspartate Aminotransferase (AST) formerly Serum Glutamic-Oxaloacetic Transaminase (SGOT)	Protein Electrophoresis
Alanine Aminotransferase (ALT) formerly Serum Glutamic-Pyruvic Transaminase (SGPT)	Routine Urinalysis
Gamma-Glutamyl Transpeptidase (GGT)	T ₃ Uptake
Alkaline Phosphatase	T ₄
Lactic Dehydrogenase (LDH)	Testosterone
Thyroid Stimulating Hormone (TSH)	Hepatitis B Surface Antigen
Prothrombin Time	Hepatitis B Surface Antibody
Serum Protein Profile	Follicle Stimulating Hormone (FSH)
Complete Blood Count (CBC)	Rapid Plasma Reagin (RPR)
Luteinizing Hormone (LH)	Sedimentation Rate
	Fecal Occult Blood

Immunologic Laboratory

Cell Surface (Phenotype) Analyses
Lymphocyte Mitogen (PHA) Stimulation Assays
Mixed Lymphocyte Culture (MLC) Fresh
Natural Killer Cell Assay by Specific Cellular Cytotoxicity Using K-562
Target Cells
Natural Killer Cell Assay (Using Interleukin-2) by Specific Cellular
Cytotoxicity Using K-562 Target Cells

test forms were developed for the 1987 followup to facilitate accurate recording and transcription; specific clinical criteria were formulated to require consultation by an allergist; and the skin test measurement criterion for possible anergy, consistent with current World Health Organization guidelines, was adopted for the clinical interpretation of all skin test readings. It was anticipated that this clinical quality control program would standardize both readings and interpretations, and would produce a uniformly superior data set.

In 1985, participant rapport-building techniques were added to boost participation in future followup studies, such as participant critique forms and recreational opportunities afforded to any accompanying family members. These were continued for the 1987 followup, and additional aspects such as unscheduled time for the participant and a number of preventive medicine evaluations including tonometry, vision screening, audiometry, and hemocult testing were added. For those testing hemocult positive, the opportunity for a proctosigmoidoscopic examination at no cost to the participant was offered.

CONDUCT OF EXAMINATIONS

All examinations were conducted in accordance with the Examiner's Handbook, provided in Appendix B, from May 1987 to March 1988. Except for weeks with national holidays, two groups of participants, averaging about 29 per group, were examined weekly. Due to the number of participants who refused the examination because of weekday business commitments or because of single-parent responsibilities, one special weekend examination was arranged late in the examination cycle. The examination was identical to the regular 2-1/2-day process, except that it was compressed into 2 days by reducing the number of participants in the group.

The logistics effort required in contacting, transporting, and examining 2,294 study members was formidable. Preexamination contacts consisted of the telephone calls for recruitment to the examination and to determine whether special requirements existed (e.g., wheelchair assistance, weekend examination schedule), and calls to arrange transportation. Once scheduling was reasonably firm, the SAIC logistics coordinator sent each participant a detailed information package outlining dietary requirements, a hemocult kit, inbriefing schedules, important telephone numbers, a request for medical records, and local maps designating examination-site eating and recreational facilities.

The logistical flow of the entire examination process was complex. Figures 4-1 and 4-2 outline participant flow for the first 2 examination days. As depicted in these figures, each group of participants (generally containing equal numbers of Ranch Hands and Comparisons) was transported early in the morning to SCRF on the first 2 days in a fasting state; tobacco, alcohol, and coffee abstinence for at least 7 hours were also required. Following initial inbriefing and blood draw on the first day, each participant was randomly assigned to the examination group or to the psychological testing group. On the second day, these groups were reversed. After randomization, each member was given an individualized 3-day schedule outlining his medical, interviewing, and laboratory appointments. The schedule carefully noted the specific required periods of fasting and tobacco abstinence (see Figures 4-1 and 4-2

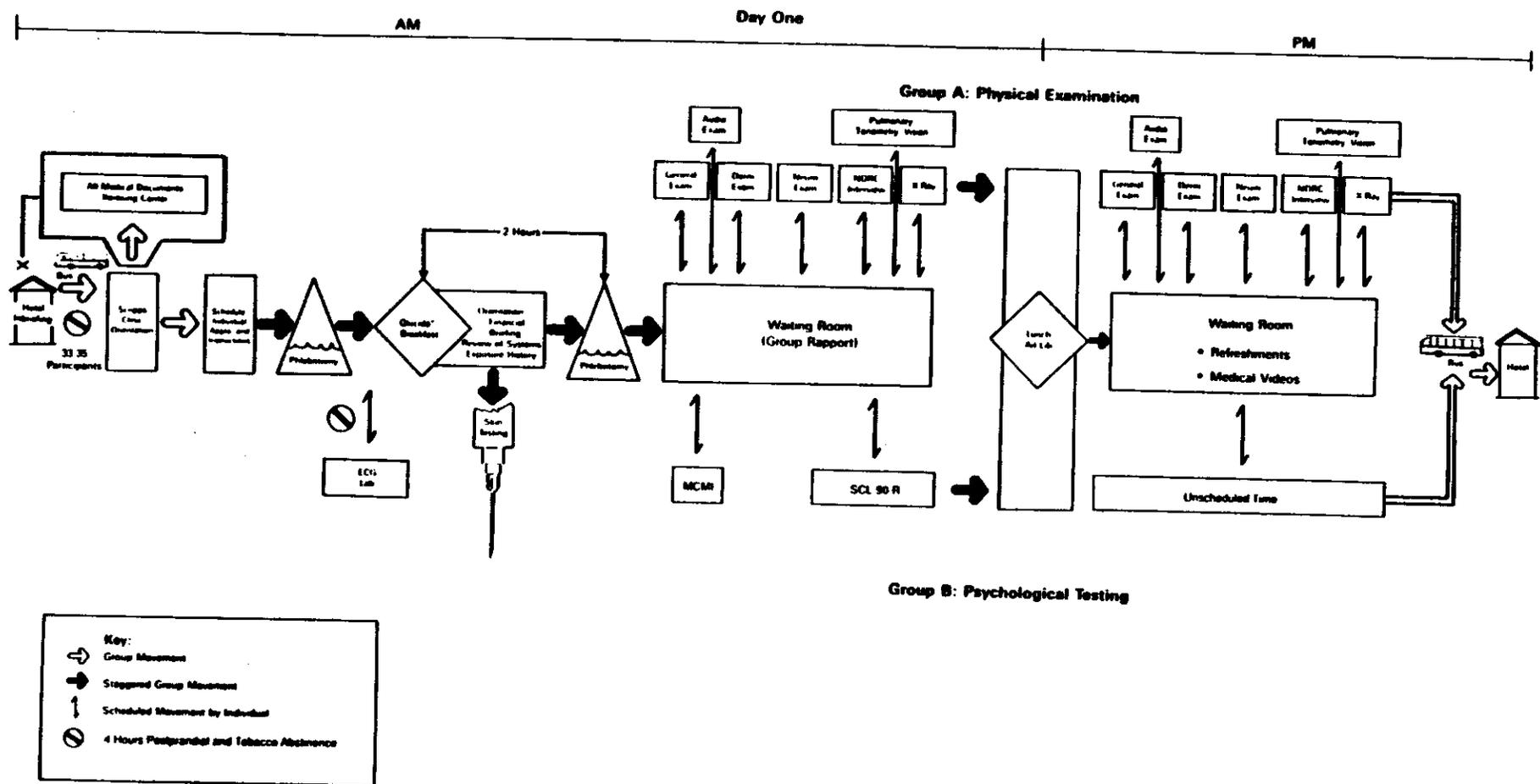


Figure 4-1.
Flow Diagram of Day One Followup
Interview and Physical Examination

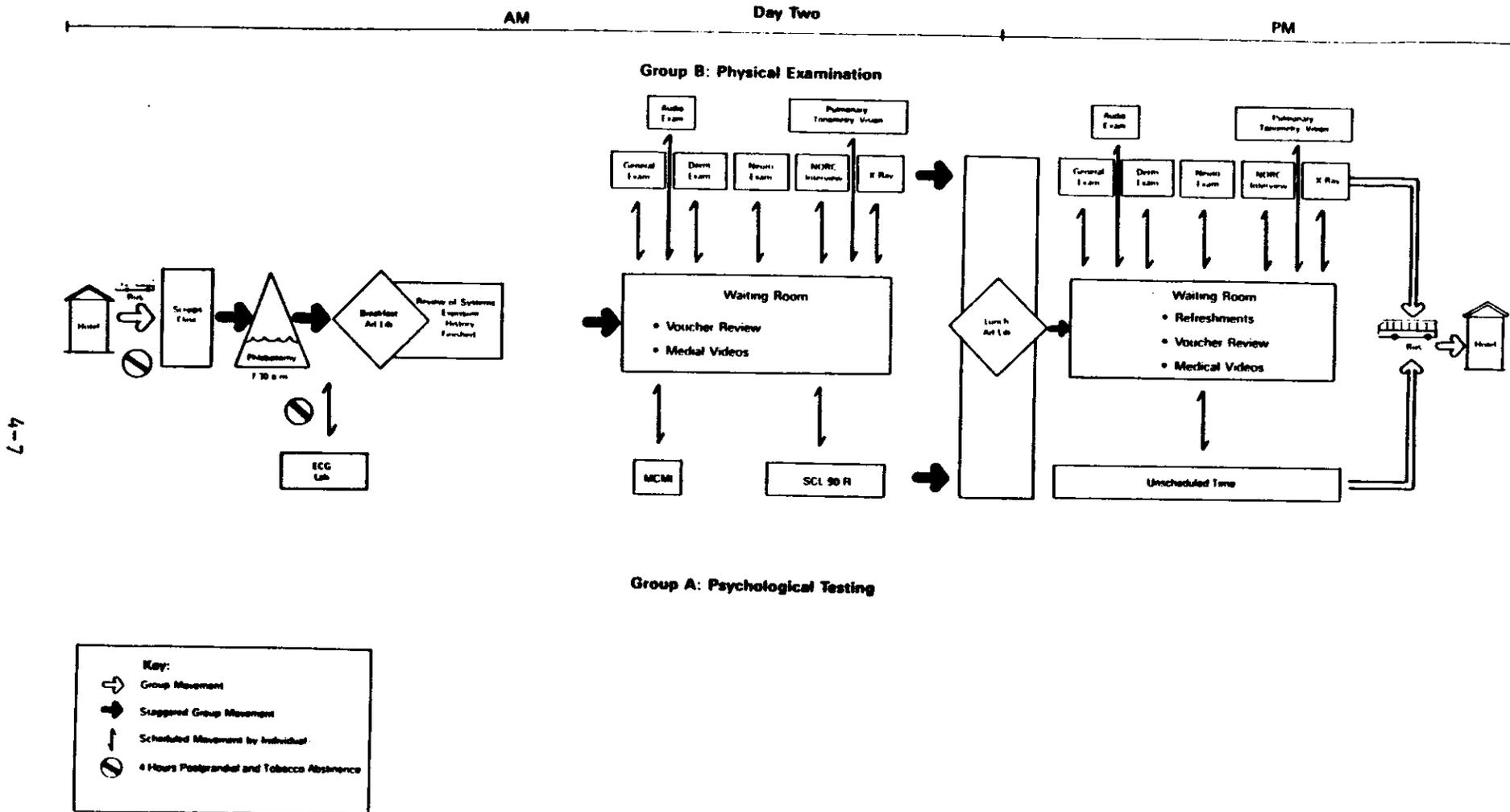


Figure 4-2.
Flow Diagram of Day Two Followup Interviews
and Physical Examination

for generalized periods in relation to electrocardiograph testing). Each individual was reminded of the fact that all aspects of the examination were strictly voluntary, and that refusals would be honored without question. Both general and specific consent forms (e.g., skin biopsy), approved by the Air Force, were explained in detail.

As in the 1985 examination, great reliance was placed upon each individual to find the appropriate clinic area at his scheduled time. This approach had great appeal to this self-reliant population as evidenced by critique feedback. Throughout the examination day, generous time was provided for waiting-room activities, i.e., renewal of past friendships, discussions of experiences in SEA, consumption of refreshments when permitted, and completion of paperwork. Day 3 of the examination was largely spent in finishing up the specialty examinations and receiving the outbriefings from a psychologist and medical diagnostician. Only upon completion of these important debriefings were the participants paid their stipend, reimbursed for travel expenses, and transported to the airport.

As noted previously, the SCRF clinical team was hand-picked for participation in this project. In total, 15 board-certified physicians in internal medicine, neurology, and dermatology participated in the general, specialty, and diagnostic examination. Involved in the performance and interpretation of laboratory testing were 10 radiologists, 3 gastroenterologists, 3 allergists, 5 pulmonologists, and 2 cardiologists. To reduce observer variability, turnover in the clinical and paramedical staffs was minimized during the 10 months of examinations. One SCRF physician served as the Project Medical Director, responsible for the scheduling, conduct, and quality control of the examinations. All examining physicians were introduced to the mark-sense examination forms during the pretest examination. The layout of the form was designed to parallel the flow of the clinical examination so as to minimize recording errors. Because data transcription was not permitted, each physician was responsible for filling in the bubbled form. To a large extent, these mark-sense forms and subsequent quality control were the primary reason for a remarkably clean data set. A complete set of forms is provided in Appendix B.

For the 1987 followup, the special testing included delayed hypersensitivity skin tests and immunologic tests. Skin tests for four antigens were administered in a standardized manner: Candida (1:1,000 weight/volume, 0.1 ml intradermal), mumps (2 complement-fixing units), Trichophyton (1:1,000 weight/volume, 0.1 ml intradermal), and staph-phage lysate ($6-9 \times 10^6$ colony-forming units of S. aureus and $0.5-5 \times 10^7$ staphylococcus bacteriophage plaque-forming units). Allergy-immunology nurse specialists measured the indurations by the standard pen method* at 48 hours after injections. For unusual cases of energy or severe local reactions, physician consultation was provided. Detailed immunologic testing (see Table 4-2) was conducted on approximately

*Starting 1 to 2 cm away from the margin of the skin test reaction, a medium ball point pen is used to trace a line toward the center of the skin test reaction. When the line reaches the margin of the area, resistance is incurred, and the line is stopped. A similar line is drawn from the opposite direction of the first line. The distance between the two lines is measured.

40 percent of the participants. By the use of the terminal digits of the study numbers that were used for previous testing, a longitudinal connection was established between examinations for these participants. Workload factors mandated blood draws on day 2 for one-half of the selected group. These individuals were excluded from skin testing to avoid interference with the immunologic results. The immunologic tests were subjected to highly structured quality control procedures set forth by the Air Force in an effort to ensure data quality. Every data point was extensively evaluated for validity and quality control.

Two other noteworthy examination features, which were implemented in 1985, were used in the 1987 followup. Because of the high proportion of adverse reactions at the first blood draw during the Baseline examination and their adverse effect upon the flying status of many of the participants, reclining blood-bank chairs were used for all phlebotomy procedures. Further, for the several serious illnesses diagnosed as a result of the examination, personal calls were made by the diagnostician to the participant's personal physician to convey accurately all of the medical findings. This consultation was followed by an immediate letter that included appropriate supporting medical data.

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REFERENCES

1. Patterson, D.G. Jr., L.L. Needham, and J.L. Pirkle. Correlation between serum and adipose levels of 2,3,7,8-tetrachlorodibenzo-p-dioxin in 50 persons from Missouri. Archives of Environmental Contamination and Toxicology 17:139-143.