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# SUBMISSION TO THE SCIENTIFIC ADVISORY COMMITTEE

## AUSTRALIAN VETERANS HERBICIDE STUDIES

3rd Meeting to be held in Sydney
3 & 4th March 1981

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SECTIONS:

1. Pilot Study Proposal

2. Progress Report on Exposure Estimation

3. Revised Plans and Estimates for the Study

SECTION 1

# PILOT STUDY PROPOSAL

# 1. AUSTRALIAN VETERANS HERBICIDE STUDIES

## 1.1 Background

In its report of its second meeting held in Sydney 14th September, 1980 the Scientific Advisory Committee (SAC) considered a research protocol which set out the broad long-term strategy proposed by the investigators from the Commonwealth Institute of Health. The Committee reported that it "considered these planned investigations to cover fairly completely the possibilities for epidemiological investigation in Australia of the effects of herbicide exposure in Vietnam during the Vietnam war". The Committee identified measurement of exposure to herbicides and the comparability of Vietnam veterans and a proposed control group as two key issues which must be clarified before the scientific viability of the whole study could be assessed. The Committee also recommended expanded pilot studies to provide the data necessary for a fully informed choice of the best method within a spectrum ranging from a mailed self-administered questionnaire (SAQ) to interview and medical examination of all veterans and their progeny. It was considered that as far as possible these preliminary investigations should be incorporated into a single pilot study to avoid the delays of a sequential approach. It was noted that there may be advantage to all concerned if the Committee were to review plans for the pilot study prior to their commencement.

Work is currently proceeding according to a plan drawn up for the pilot survey. Due to limited resources in personnel and shortage of time it has not been possible to provide completed documentation for all aspects of the pilot study. The present submission is a summary which has been prepared to meet a deadline. Further development, particularly of data collection instruments, is proceeding rapidly and more information could be made available to the Committee during its meeting, if so desired. A progress report on exposure estimation is submitted in section 2 and revised plans and estimates for the investigation are submitted in section 3.

## 1.2 Postulated effects of herbicides*

The terms of reference as given by the Department of Veterans' Affairs to the now Commonwealth Institute of Health concerned the possible effects of contact with or exposure to Agent Orange and subsequent disabilities in Australian veterans, or in complications of pregnancy in their spouses and the occurrence of congenital malformations in their offspring. Although the possible effects of Agent Orange remain the primary concern of the investigators, the possible effects of exposure to other herbicides such as Agent Blue (cacodylic acid) will also be actively sought in the investigation.

Agent Orange consisted of a mixture of 2,4-D and 2,4,5,-T. The latter is contaminated during manufacture with TCDD (2,3,7,8-tetrachlorodibenzo-para-dioxin). The pharmaco-dynamics and toxicology of these chemicals has recently been reviewed by the Department of Health. 2,4-D may be absorbed from the gastrointestinal tract or by inhalation. Little absorption occurs directly though the skin. Absorbed 2,4-D is quickly excreted from the body, mostly in urine as the free acid. It does not accumulate in the body. There are many reports of consumption of sublethal doses of 2,4-D without any apparent ill-effects. However, occupationally exposed workers have complained of non-specific symptoms such as excessive fatigue, epigastric pains, anorexia (loss of appetite), occasional upper respiratory tract symptoms and impaired taste sensitivity. Medical investigation has not implicated 2,4-D as the cause of all symptoms but did suggest indications of increased incidence of liver disease among workers with chronic exposure to herbicides. Isolated cases of peripheral neuropathy and contact dermatitis following exposure to 2,4-D have been reported.

2,4,5-T is readily absorbed from the gastrointestinal tract after ingestion and probably after inhalation. Skin absorption, however, is slight. Like 2,4-D it is readily excreted and is not stored in the body. Some metabolism does occur in animals but the bulk is secreted unchanged in the urine. The oral dose required to produce symptoms in man is probably three to four grams. Medical examination of workers engaged in the manufacture of 2,4,5-T has shown increased incidence of chloracne which could be attributed to the presence of TCDD as an impurity. It should be noted that increased incidences of urinary porphyria, chloracne and hirsutism have been demonstrated in workers employed in manufacturing chlorinated phenols such as 2,4,5-trichlorophenol, the precursor of 2,4,5-T. Again, the responsible agent could be TCDD, and most reports do not distinguish its effect from possible effects of 2,4,5-T. 2,4,5-T has been shown to cause teratogenic effects in animals which cannot be wholly attributed to the presence of toxic impurities such as TCDD. Whether or not 2,4,5-T is carcinogenic cannot be deduced conclusively from results reported to date.

2,4,5-T, like 2,4-D, does not increase mutation rates nor stimulate mutagenic responses in rats and mice. It does, however, produce chromatid abnormalities *in vitro* in cultured human lymphocytes and affect the chromosomes and reproductive mechanisms of mouse and hamster bone marrow cells. It should be added, however, that these effects may have been due to cellular toxicity rather than genetic alteration.

* Information in this section has been obtained mainly from unpublished documents prepared by the Department of Health, Canberra.

TCDD was present in Agent Orange and Agent Purple used by U.S. military forces in South Vietnam. Knowledge of the toxic effects of TCDD in man comes mainly from medical assessment of occupationally exposed workers engaged in the production of chlorinated phenols and their derivates. Limited data are available from known episodes of exposure of the general population. Table 1.1 lists known toxic effects attributed to TCDD in man.

TABLE 1.1 TOXIC EFFECTS OF TCDD IN MAN

| | |
|---|---|
| Dermatological: | Chloracne |
| | Porphyria cutanea tarda |
| | Hyperpigmentation and hirsutism |
| Internal: | Liver damage (mild fibrosis, fatty changes, haemofuscin deposition and parenchymal-cell degeneration) |
| | Raised serum hepatic enzyme levels |
| | Disorders of fat metabolism |
| | Disorders of carbohydrate metabolism |
| | Cardiovascular disorders |
| | Urinary tract disorders |
| | Respiratory tract disorders |
| | Pancreatic disorders |
| Neurological: | Polyneuropathies |
| | Sensory impairments (sight, hearing, smell, taste) |
| Psychiatric: | Neurasthenic or depressive syndromes |

Source: Homberger, E. Reggiani, G. Sambreth, J. and Wipf, H.K., Ann. Occup. Hyg. 22, 3273 (1979)

Exposed individuals may develop a variety of medical conditions with chloracne, neurological and behavioural changes, liver and fat metabolism disorders and signs of porphyria cutanea tarda (a disorder of porphyrin metabolism) among the most frequently reported toxic effects. Reports from Sweden have shown recently a statistically significant association between human exposure to chlorophenoxy acids and chlorophenols and increased incidence of certain soft tissue sarcomata and lymphomata.

Table 1.2 summarises the results of some toxicological experiments with TCDD in laboratory animals.

TABLE 1.2 TCDD - EXPERIMENTAL TOXICITY

| | Dose (1) |
|---|---|
| $LD_{50}$ for laboratory animals | 1 (0.6-115)ug/kg |
| Systemic lesions (liver, blood, skin, etc) and clinical chemistry abnormal findings at chronic administration | 0.1 ug/kg |
| Embryotoxicity, foetotoxicity, postnatal growth retardation | 0.25 ug/kg |
| Reproduction, fertility | 0.01 ug/kg |
| Immunodeficiency (atrophy of lymphoid tissue) | 0.1 ug/kg |
| Enzyme induction | 1 ug/kg |
| Carcinogenicity | 0.1 ug/kg |
| Mutagenicity (?) | 2 ug/ml |

(1) Indicative values

Note: lug = 0.001mg

Source: Homberger, E. Reggiani, G. Sambreth, J. and Wipf, H.K., Ann. Occup. Hyg. 22, 3273 (1979)

Chronic toxicity of TCDD is most often manifested as hepatic necrosis (death of liver cells) and thymic and lymphoid atrophy. The degree of hepatic involvement appears to be dose and species related. Supression of the thymus and lymphoid tissue leads to decreased immune responses in mice, rats and guinea pigs. Acne of increasing severity was produced when increasing doses of TCDD were applied to rabbit's ears. A total dose of 0.002 to 0.003 mg/kg over a nine month period produced severe haematological changes and death in rhesus monkeys, making these among the most TCDD-susceptible animals tested.

TCDD is a potent teratogen which causes increased fetal mortality in animals. It produces cleft palate and kidney abnormalities in mice at doses as low as 0.001 mg/kg whilst depressed fetal weight and visceral lesions occur in rats at 0.0005 to 0.001 mg/kg. Teratological effects in rhesus monkeys have not been demonstrated. Studies on the carcinogenic potential of TCDD have been less conclusive. The potential mutagenicity of TCDD in humans has not been determined. Feeding studies with rats have not shown mutagenic effects but TCDD has been shown to induce mutagenic changes in some strains of bacteria, in common with many other substances.

Cacodylic acid

When used as a herbicide cacodylic acid has the potential for absorption by inhalation and through the skin. No human data are known to be available on its dermal absorption and very little is known about human pulmonary absorption of organic arsenicals. Ingested seefood arsenic is apparently absorbed from the gastrointestinal tract. Whilst no data are available on the distribution of organic arsenic compounds in humans, studies with forestry workers exposed to cacodylic acid have demonstrated its rapid urinary clearance form the body.

Study of the biotransformation of cacodylic acid in living rats has shown that it is fairly stable in vivo and is not converted to inorganic arsenic. Any in vivo transformation of cacodylic acid in other species is not clear. Little data are available on the chronic toxicity of cacodylic acid in humans. Toxic effects of these organic arsenicals used as drugs are mainly manifested in the central nervous system and include encephalopathy and optic atrophy. Other less frequent side effect include dermatitis, liver damage and disturbances of the haemopoetic system. Cacodylic acid has been considered as a source of intoxication of domestic animals leading to symptoms similar to those produced by chronic ingestion of inorganic arsenic. Chronic feeding of cacodylic acid to rats and beagle dogs has produced no significant effects on body weight, food consumption, organ weights, urinalysis or haematological system.

Organic arsenicals have no known mutagenic or teratogenic effects in man or animals and no conclusive evidence of carcinogenic activity in laboratory animals is known. No epidemiological investigations are known to have been conducted on the carcinogenicity of cacodylic acid or other organic arsenic compounds.

There are only three reported studies of the toxic effects to humans of cacodylic acid and its salts in the recent literature. The most extensive documentation of cacodylic acid toxicity in humans is that of Peoples et al. (1979). These authors reviewed 34 uncontrolled cases of occupational exposure amongst Californian agricultural workers which occurred between 1975-79. Exposure occurred as a result of misuse, accident or equipment malfunction. Basically, cacodylic acid acted as a chemical irritant. Ingestion produced nausea, colic vomiting and diarrhoea. Application to the eye produced mild conjunctivitis whilst dermal application produced a contact dermatitis or an allergic response. The worst case was that of a spray-rig operator who received particularly heavy exposure by drenching of his clothing and by splashing of herbicide solution into his mouth. He was hospitalised with "paralysis, irregular respiration, numbness and fainting". Investigation revealed no organ damage and recovery was spontaneous. Full recovery was always prompt in the other cases, and blood arsenic levels always remained normal. No chronic effects were reported.

Inorganic Arsenic Compounds

Chronic exposure to medicinal inorganic arsenics such as Fowlers' solution produces a characteristic syndrome of hyperpigmentation followed by keratoses and, infrequently, dermal neoplasia. This distinctive clinical syndrome has lead to general agreement that arsenic can cause skin cancer. There have been numerous reports and several epidemiological studies of the incidence of cancer amongst workers occupationally exposed to arsenic in mining and metallurgy, in the chemical industry and in agriculture. The epidemiological data are consistent with but do not demonstrate a causal relationship between inorganic arsenic and cancer of the skin and respiratory tract.

There is nothing in the recent literature to suggest that cacodylic acid is degraded to inorganic arsenic in vivo. Indeed there is ample evidence that such a process would be contrary to the established metabolic fate of arsenic compounds in mammals.

Maldiosin (Malathion)

Maldiosin is an organophosphorus insecticide of moderate mammalian toxicity. It is rapidly metabolised to a variety of products and excreted largely in the urine. It is not cumulative in body tissues. Sublethal exposure can cause depression of plasma colinesterase activity but this requires a high intake. Spontaneous recovery occurs after cessation of exposure.

Other insecticides used in Vietnam include DDT. The chronic toxicity of DDT to man has been thoroughly investigated. Massive chronic exposure produces only a mild stimulation of the microsomal enzymes of the liver.

In this investigation the major postulated effects are those related to TCDD, since this is the potentially most toxic contaminant in Agent Orange which comprised a very high proportion of herbicide used in Vietnam.

## 2. AIMS AND OBJECTIVES OF THE PILOT STUDY

### 2.1 General Aims

The purpose of the Pilot Study is to assist in planning the main survey. It addresses methodological issues related to study design including the comparability of Vietnam veterans and the proposed control group and, methods of data collection. It is not expected to provide data on the effects of herbicide exposure in Vietnam but is expected to test methodology and provide a basis for logical decision as to the best and most acceptable methods of the conducting the main survey.

### 2.2 Specific Objectives

The specific objectives of the pilot stuoy are as follows:

2.2.1. To chose between several methods of data collection.
The choice will be made primarily on the response rate and quality of data, although the cost and duration of data collection will also be a consideration.

2.2.2. Comparability of Veteran and Control Groups
The pilot study will obtain data on comparability additional to that available a priori from existing records.

2.2.3. Test of Procedures to be used
As far as possible the procedures to be used in the family survey will be tested during the pilot study. The greatest emphasis will be on data collection and analysis related to the specific objectives of the pilot study.

## 3. RESEARCH PLAN

### 3.1. Vietnam Veterans and Control Groups

1. About 40,000 male army personnel served in Vietnam. About 11,000 male personnel served in the Army during the period of the Vietnam War but were not sent to Vietnam. It has been decided to restrict the study at this stage to male Army personnel for the following reasons:

(a) To avoid the introduction of possible confounding factors. This means the veteran and control groups should be as homogeneous as possible. The minimal medical standards of entry into the three Forces were not the same. The Army had a far larger contingent of National Servicemen than either the Navy or Air Force and the usual Service experiences (e.g. diet, living conditions, combat conditions) of members of each Force were presumably quite different. It was therefore decided to draw the veteran and control groups from within a single Force.

(b) The possible herbicide effects could be very small. As large as possible a sample of veterans and controls should be considered so as to maximise the chances of detecting such effects. The Army was the largest Force and also contained the highest number of potentially exposed individuals. It was therefore preferred to the Navy or Air Force.

(c) There are only a few hundred potentially exposed female Army personnel. Because of marriage and the subsequent change of surname it would be difficult to contact these individuals. Furthermore, even if all could be contacted a few hundred is too few for the likely detection of the types of effects to be considered in the family survey. It was decided to restrict the study, at least initially, to male servicemen.

Australian involvement in Vietnam ceased at the end of 1972. It was decided that only male servicemen who enlisted pre-1973 and who served in the Army at some period during the Vietnam War years would be included in the study. Of this group those who went to Vietnam will be known as the V group, those who did not will be known as the C group.

### 3.2. Comparability of Groups

Before undertaking a statistical analysis of the possible effect of herbicide exposure, it is necessary to compare the V and C groups. Significant differences between the groups should be noted and, where possible, corrected for in the final analysis. To date it has been possible to compare the V and C groups on the basis of age at enlistment, time spent in Army and National/Regular service. The two groups are statistically significantly different ($p < 0.01$) with respect to each of these three variables. Figure 1 illustrates the results.

The difference in the age at enlistment distributions of the V and C groups (fig 3.1 (a)) is due to the fact that, although there are none of the C group in the GE 3$ category, there are 417 of the V group in this category. In the other 4 age at enlistment categories about 85% fall in the V group and 15% in the C group. The effects of age are well-documented in the epidemiological literature and it should be possible to adjust for this difference.

Figure 3.1 (b) shows that, for the V group there is a higher percentage of Regular servicemen than of National servicemen. Exactly the opposite is true of the C group. It is not so obvious how one should adjust for this difference between the groups. This matter needs close attention. The psychological scores in the entrance medical exam could be of assistance in this regard as could further information to be obtained via the pilot study questionnaires.

Figure 3.1 (c) shows that the V group is different from the C groups in so far as a much larger proportion of the former remained in the Army for more than six years (this being the shortest optional sign - on period for a Regular serviceman). This difference is probably largely attributable to the fact that more of the V group were Regular servicemen making a career of the Army. However other effects could also be operating and the data to be collected from the pilot study should be studied closely with regard to this difference.

The results of the pilot study will be needed before the question of comparability can be addressed more fully. This will give information on other variables such as ethnicity, socio-economic status, rural/urban living, together with a self-assessment of the reason for not going to Vietnam. It is planned that Army medical records of the entrance physical examination will be used to give medical and psychological status at the time of enlistment.

3.3 Design of the Pilot Study

Twenty three Sydney metropolitan electorates have been selected. Six hundred individuals are to be drawn from these electorates, 300 from the V group and 300 from the C group. Three different interview modes (self-administered (SA), telephone (T) and face-to face (FF)) are to be assessed. One hundred individuals from both the V and C groups will be interviewed under each method.

Figure 3.2 illustrates the age at enlistment, length of service and Regular/National service profiles of the V and C subgroups in the selected Sydney electorates. These should be compared with the Australia-wide profiles illustrates in Figure 3.1. It is clear that, at least on the basis of these three variables, the chosen Sydney electorates are representative of the whole of Australia for V and C groups.

Since age at enlistment, length of service and Regular/National service status have been shown to be important variables, it was decided to stratify when selecting the pilot survey sample. To ensure that there are a sufficient number of individuals in each stratum, some of the data have been grouped. Subject to the contraints imposed by the overall numbers available in the chosen Sydney electorates in each stratum, the design has been chosen to be as "balanced" as possible with respect to the V and C groups. Table 3.1 below shows the numbers to be sampled from each stratum

Table 3.1: Number of Veterans and Controls to be selected at random from each stratum by service status and time in the Army.

| Service Status | Time in Army | Vietnam (V) | | non-Vietnam (C) | |
|---|---|---|---|---|---|
| | | Age at enlistment | | Age at enlistment | |
| | | LE 20 | GT 20 | LE 20 | GT 20 |
| Regular | GT 2 yr. | 38 | 42 | 48 | 43* |
| Army | LE 2 yr. | 38 | 42 | 40* | 16* |
| National | GT 2 yr. | 37 | 25* | 14* | 2* |
| Service | LE 2 yr. | 37 | 41 | 48 | 89 |
| MARGINAL TOTAL | | 150 | 150 | 150 | 150 |

* the maximum possible number so far indentified as resident in the Sydney study area.

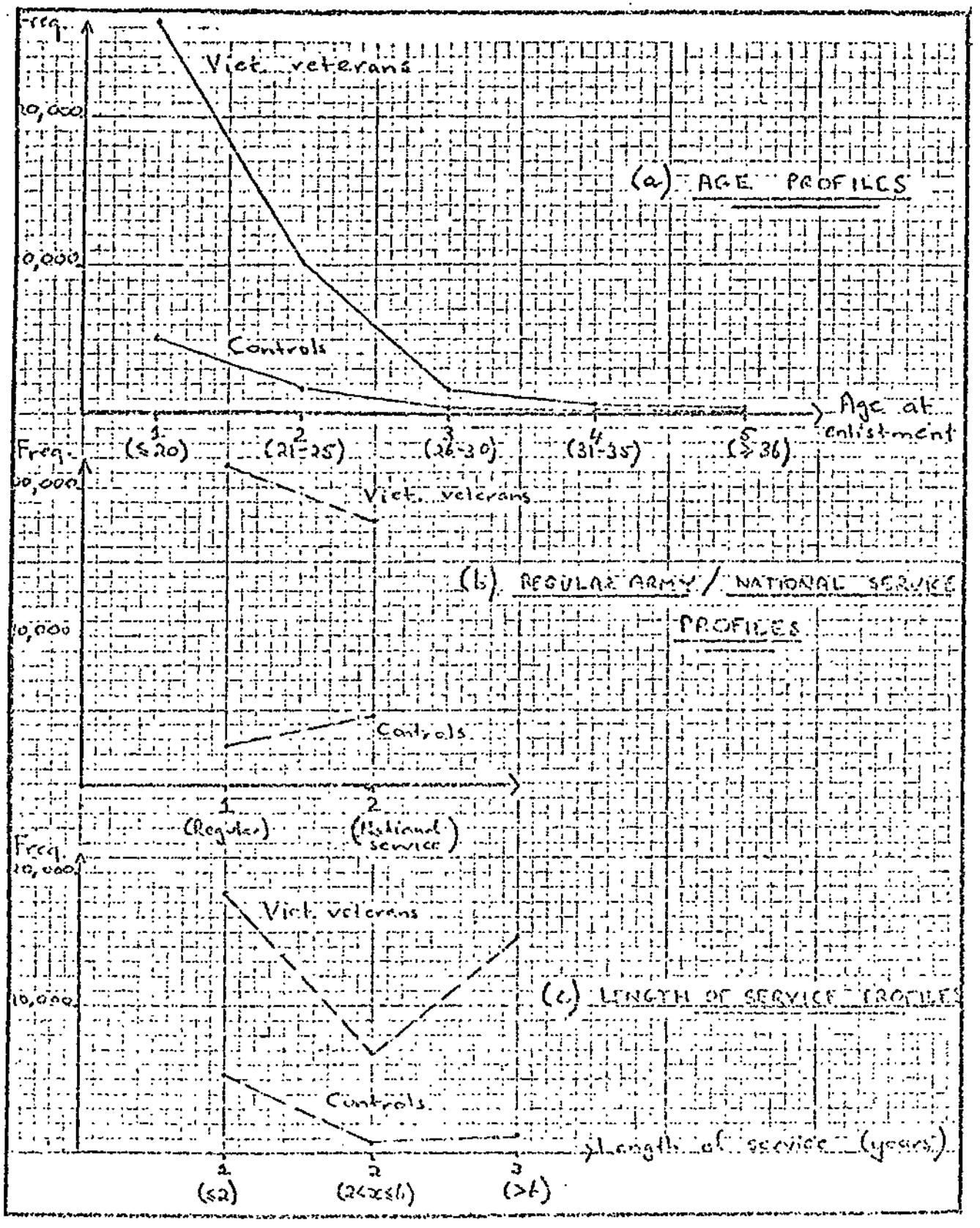



Figure 3.1 Profiles by (a) age, (b) service status and (c) length of service for the total population of the V and C groups in Australia.

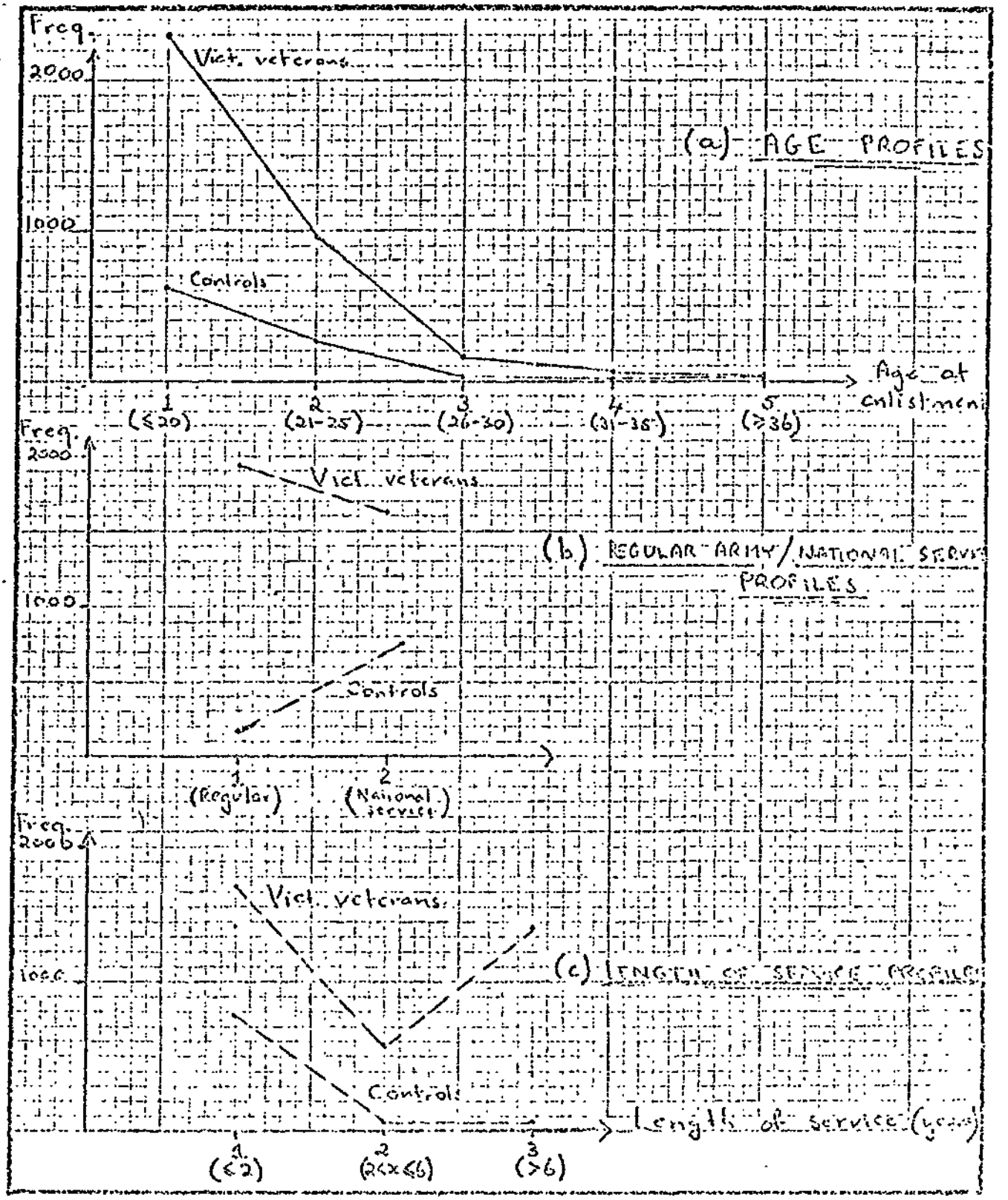



Figure 3.2 Profiles by (a) age, (b) service status and (c) length of service for the population to be sampled in the Pilot Study.

## 4. METHODS OF DATA COLLECTION TO BE TESTED FOR THE FAMILY SURVEY

### 4.1 Data Collection Methods to be Tested

Four different methods of data collection are to be tested in the pilot study giving a total of five different data sets for analysis. They are:

1. Self-administered questionnaire
2. Telephone interview
3. Face-to-face interview
4. Telephone interview and medical examination
5. Face-to-face interview and medical examination.

The same questionnaire will be used for methods 1, 2 and 3. Differing additional instructions, standard probes and explanatory remarks will be issued for the questionnaire for each of methods 2 and 3. The questionnaire is divided into two booklets - one for the male, the other for his wife.

The one questionnaire also serves veterans and controls. The areas of the questionnaire not applicable to controls are clearly designated.

The mailing initiating the self-administered questionnaire, telephone interview and face-to-face interview will take place on the same day. A mailing house will be used for the pilot study as this will be necessary in any type of family survey.

### 4.1 1. Self-administered questionnaire

The two questionnaires, two postage paid return addressed envelopes and two questionnaire comment slips will be mailed together with an individually addressed covering letter. A reminder letter, together with another set of questionnaires, comment slips and return envelopes will be sent $2\frac{1}{2}$ weeks later to non-responders. Ten days later, again, continued non-responders will be contacted by telephone reminder call and a door-knock reminder will be made about 12 days after that. There will be no deviation from the self-administered approach. Neither telephonists nor door-knock interviewers may conduct the interview.. The door knocker may take delivery of the questionnaire.

### 4.1 2. Telephone interviews

An individually addressed letter will be mailed to each veteran together with two slips (on which he and his wife will suggest the best times and telephone numbers at which they can be contacted) and two postage paid addressed return envelopes. Telephone interviewing will take place as the return slips are received. Non-responders will be contacted by means of a printout provided by Telecom or by consulting telephone directories. Those without telephones will be door-knocked and interviewed face-to-face.

### 4.1 3. Face-to-face interviews

Initial contact will be by means of an individually addressed letter explaining the study and that an interviewer will call or telephone to make times for the interviews. The man and wife will be interviewed at times and places convenient to them.

In all three methods an attempt will be made to get non-responders to complete a mini-questionnaire including brief health details and the reason for non-response.

4.1 4. Telephone interview plus medical examination

On completion of the telephone interview, the interviewer will offer, to a pre-selected sample, the medical examination. Family preference for location and time will be noted.

4.1 5. Face-to-face interview plus medical examination

On completion of the face-to-face interview the interviewer will offer to a pre-selected sample the medical examination. Again the family preference for location and time will be noted.

Appointments for the examination will be finalised from the Study office.

The entire fieldwork period from the mailing date to cut-off is two calendar months.

4.2 The questionnaire

The broad objectives of the questionnaire are:

- To collect all data that may be relevant. Areas to be covered are exposure to herbicides, serviceman's medical disorders, family birth defects, female reproductive histories, possible confounding factors, comparability of veterans and controls:
- To collect valid data.
- Upgrade personal details for continued subject surveillance.
- Ease of management and administration.
- To facilitate easy entry into computer and the subsequent editing.
- To collect relevant data to categorise individuals for each disorder.
- To attract and hold the interest of the subject.

It has been possible to design one questionnaire, which contains the items deemed necessary to achieve these objectives, that can successfully be both self- and interviewer-administered. The use of the standard questionnaire also allows for exact statistical analysis of the quality of data between methods and removes a variable from the assessment of response rates. Individual items have been designed to cover one or more of the following data areas:

- general demographic
- socioeconomic
- comparability of veterans and controls
- confounding factors
- long-term surveillance of the veteran
- exposure to herbicides
- medical status of veteran
- reproduction in women
- birth defects in children.

Available literature and experience suggested that the male subjects would not adequately answer questions on reproduction in their wives, birth defects in their children nor be able to give the names and addresses of attending doctors or hospitals. It was, therefore, decided to provide one questionnaire for the man and a shorter separate questionnaire for his wife to provide details of her reproductive history and any birth defects in her children (details of the structure of the questionnaire are appended in 10.1).

The internal design of the questionnaire has considered:

- The number of questions. Only those needed to gain necessary data have been included. No areas of interest are omitted.

- Question design. The questions are simply worded; easily understood; not open to interpretation; allow for and cover all possible answers to each question.

- Length. The questionnaire is of reasonable length with no unnecessary areas.

- The order of questions is logical and tactful.

- The subject's task is straightforward, simple and remains constant for closed questions.

- The instructions and explanations to the subject or interviewer are adequate and clear, friendly and occur as frequently as necessary.

- Coding provisions are clear and accurate and allow for speedy operation.

- Non-coded questions provide well-designed space for writing open-ended answers and the coding plan provides for the ultimate coding.

- The skip instructions follow one system only. As both veterans and controls are using the same questionnaire clear definition has been provided where questions are not relevant for controls.

- Comparability. Where possible and appropriate the questionnaire provides for comparability with other relevant studies.

## 4.3 Data Collection for Questionnaire

### 4.3.1 Interviews

Standard explanations, probes and extra question leads will be written into the questionnaires used for both telephone and face-to-face interviews. A questionnaire manual, specific interviewing manual and a coding manual will be issued.

### 4.3.2 Interviewers

The telephone interviewing, face-to-face interviewing, telephone reminder and door-knock reminder burden of the pilot study is to be contracted to an interviewing consultancy. Only firms capable of undertaking the family survey will be considered. The consultant will be required to provide female interviewers of the highest standard and experience. Close field supervision will be mandatory to ensure correct interviewing techniques, quality control of data and standard approach.

In addition information will be provided by the consultant on fundamental comparability matters such as time taken for interview, number of calls (telephone, in person) to achieve interview, rapport, relative costs, times of day and week contacts were established. Each respondent will be asked to complete the subject's comment sheet, which was mailed with the questionnaire, to gain direct information from each subject about his or her feelings about the questionnaire and the study in general. After each telephone and face-to-face interview the respondent will be asked these questions also. Further feedback about the pilot study, the questionnaire and the data collection method will be gained in debriefing sessions with interviewers and their supervisors.

## 4.4 Coding and Data Entry for Questionnaire

### 4.4.1 Coding

Where the possible range of answers to a question can be anticipated, the question is pre-coded. Where tables of responses occur, the coding scheme is pre-planned. Alphabetical punching will be used where coding is impossible and where absolute accuracy of recording is needed e.g. names and addresses of subject's doctors and hospitals. Coding schemes for open-ended questions will be devised from the pilot study questionnaire data. The questionnaire is designed so that no rewriting nor transcription of coded answers is required.

Self-administered questionnaire

The subject will tick pre-coded boxes or write answers in full. These completed schedules will be edited and postcoded by study staff.

Telephone and face-to-face interviews

The interviewer will automatically code each reply except those requiring postcoding which will be done in the office.

### 4.4.2 Data Entry for Questionnaire

The questionnaire layout is designed so that this can be done straight off the questionnaire.

## 4.5 Medical History and Medical Examination Development

The medical examination is being developed in order to examine 200 families, 100 of whom will be controls and 100 will be veterans. 100 of the families have been interviewed by telephone and 100 face to face.

The medical examination is planned to be the same in essentials in the pilot study as any medical examination that may be conducted in the main survey of families.

### 4.5.1. Objectives

The objectives of the medical examination in the pilot study are:

1. To compare the methods of data collection i.e. to determine if medical examination contributes to the quality of the data.

2. To help validate information obtained at interview.

3. To screen subjects for

   (i) Specific conditions - in the past or present, that could be related to herbicides.

   (ii) Present state of health.

   (iii) Indications of chronic disease that may or may not be related to herbicide effect.

4. To look for observable birth defects in the offspring of subjects.

### 4.5.2. Rationale

The conditions presently regarded by Veterans as related to herbicide exposure include:

Skin disease - particularly chloracne;
Altered Behaviour e.g. violent mood swings;
Neurological symptoms such as numbness and tingling of extremities;
Various gastro-intestinal disturbances.

Many of these complaints are subjective and difficult to measure. With this in mind the proposed Medical Examination will not be primarily disease oriented but rather symptom oriented.

It will involve a detailed Medical History in order to determine if the outcomes of interest exist, but in the context of past and present health.

Personal, family and occupational histories as well as a physical examination with special emphasis on target areas will be included.

A series of psychological tests in common use are planned in an effort to elucidate the particularly difficult area of behavioural change.

4.5.3 Facility

It is proposed that the medical examinations should take place at a centrally located public Hospital or other facility.

A team of two physicians, one paediatrician, 2 nurses and a clerk should be able to handle 4 families in the examination period which is estimated to be 3-4 hours.

The location should have laboratory, equipment, waiting room and interviewing room facilities.

The medical history and physical examination will be performed by separate physicians, while psychological tests will be supervised by nurses.

## 5. VALIDATION OF MEDICAL DATA

### 5.1 Overview

Medical record validation is planned to run concurrently with the checking, editing and coding as well as input of the data.. It is important that the validation and input phases are co-ordinated and that an even balance of work is maintained. Medical record validation will be performed by the medical record administrator (Ms. Keitha Jones) appointed to the project, with the assistance of a second medical record administrator.

### 5.2 Methodology

Upon receipt of information from 600 Pilot Study survey questionnaires, information will be checked, edited, coded and input by key punch operators.

Computer lists of all YES responses to medical questions will be generated, providing the subject has completed the section on health care facility treatment/type of facility/address of facility/approximate date of treatment.

Listings will be by subject name with groupings by health care facility to be approached.

Computer validation checklists will be generated for each subject, containing the following information;

SUBJECT'S NAME/ADDRESS/DOB/QUESTION NUMBER (YES RESPONSE) NAME OF HEALTH CARE FACILITY.

Methodology of validation of Hospital Medical Records will be as follows:

Proposed Validation Format

1. Condition investigated
2. Condition not investigated
3. Condition investigated but not validated
4. Condition investigated/condition confirmed and accounted for by known disease factors
5. Condition investigated/condition confirmed but not accounted for by known disease factors

Lists of medical records to be viewed will be sent to each hospital medical record administrator/hospital administration with a photocopy of the subject's signed consent to release information. The subject's original consent form will be retained within the Herbicide Study offices.

Each validation checklist will be coded by the M.R.A. using the International Classification of Diseases 9th Revision W.H.O. as each condition is validated.

Validator's initials and date of validation will also be entered.

## 5.3. Conditions to be validated

The following target organs/systems/conditions will be assigned specific disease codes, using I.C.D.9 for the purpose of validation. Broad I.C.D.9 groupings will be used for preliminary statistical analysis.

| TARGET ORGAN/SYSTEM/CONDITION | ICD GROUPING | ICD SPECIFIC CODES |
|---|---|---|
| Dermatological | 680 - 709 | to be decided |
| Neoplastic | 140 - 239 | |
| Hepatic | 570 - 573 | |
| Haemopoetic | 280 - 289 | |
| Immunological | | |
| (Endocrine/Metabolic/Nutrit) | 240 - 279 | |
| Cardiovascular | 390 - 459 | |
| Renal | 580 - 599 | |
| Reproductive - Male | 600 - 608 | (D.S.M. 111) (ICD 9-300-316)? |
| (Incl. Sexual) | | |
| - Female | 630 - 676 | 610-629 |
| Neurological | 320 - 389 | |

Medical record validation will also include checking hospital medical records for:

Reported deaths of offsprings )
Reported neoplasms of offsprings ) VETERANS & CONTROL
Reported Birth defects of offspring)

Reported birth defects, reported deaths/reported neoplasms of offspring will be coded using ICD 9 after medical record validation.

5.4 Service Medical Records (covering the period of Vietnam Conflict)

Army health services medical records are stored in Melbourne (separately from the Central Army Records Office) and will be viewed in order to determine:

1.1 Type of medical data available
Number of medical examinations performed
Content of each medical examination
Methods of question batteries/scoring used by the Army medical personnel
Methods of determining medical status on entry into the army
Determine who will retrieve/select 600 index cards and pre-code the information

1.2 It is proposed that the statistician and medical record administrator view and select these records for the Pilot Study

1.3 These records are stored via the last two digits of the Army service number (6 or 7 digit number depending on type of enlistment).

5.5 Non-Service Records

5.5.1 Validation using Hospital Records

5.5.1.1 In all subjects

Identification sheet/reported final diagnoses
Hospital discharge summary/concurrent final diagnoses - copy retained by M.R.A.
Operation charts
Various treatment charts
Physician's notes (past/present history of illness to be validated)
Nurses notes
Consultation charts
Laboratory charts/biochemistry - Abnormal results/x-ray/cat scans/nuclear medicine/special radiological procedures
Cancer registration notification and subsequent forms
Hospital discharge reports (cases where no discharge summary is available)

5.5.1.2. Additional sources for birth information and birth defects

Obstetrical charts/delivery charts
Newborn (reported birth defects) charts

5.5.2 Validation with General Practitioner Records

The methodology will be as for hospital medical records, refer 5.2.1 with computer validation checklists, and standard contract letter (comptuer generated) requesting validation of reported yes responses to target organ conditions.

The quality of data obtainable from G.P. records is at present an unknown factor. The retention and storage as well as retrieval methods is also an unknown factor. The R.A.C.G.P. P.O.M.R. system has been introduced to many G.P. surgeries in N.S.W. and in these cases retrieval of recent medical information should present no problems.

5.5.3. Validation with Specialist Medical Records

The methodology will be as for Hospital/G.P. records and presents the same problems of retrieval systems. Quality of data available is also an unknown factor.

5.5.4 Validation using other Medical Record Sources

1. Death certificates
2. Post mortem reports
3. Coroners Court Medical Records may be used for reported deaths by means of misadventure. These reports do not appear to be sent to hospital medical record departments as a matter of course.
4. Health Statistics Bureau
5. Perinatal Statistics Unit Commonwealth Institute of Health Sydney University - Dr. Paul Lancaster.
6. Maternal and Child Health Division of Health Commission - Dr. (Grattan-Smith)
7. Community Health Centres
8. Medibank for 1975 is an unbiased although limited source of information (as a fall-back validation instrument). Records are held by the Commonwealth Department of Health, and could possibly be used as a validation for reported diagnoses or as an independent source of data on outcome. This is being investigated further. The major problem at present appears to be retrieval of identifying information..

## 6. CONFIDENTIALITY AND PRIVACY ISSUES

### 6.1 Confidentiality

Much of the information being sought is sensitive and personal, and some may be relevant should the veteran make a future medical claim. In order to reduce non-compliance, it is essential that information collected from subjects should be used only for the purposes of the investigation, and that this can be absolutely guaranteed. A unique confidential survey number will be assigned to each subject and only this number will be used to identify data. A separate f le will be kept of names, service number and this confidential survey number.

The investigation should be required to refuse access to individual data to any other government department or organisation. A means to ensure this is currently being investigated, one possibility being that members of the study team should have the status of Census Officers.

### 6.2 Privacy

Medical record administrators constantly face the problem of balancing the desire for personal privacy against the need for public/research information. In many situations a great deal of personal discretion is used, since legal precedent is practically non-existent.

#### 6.2.1 New South Wales Privacy Committee

The New South Wales Privacy Committee was established under the Privacy Act, 1975 (N.S.W.) as a direct result of Professor W.L. Morrison's Report on the Law of privacy (1973). The 13 members of the Privacy Committee have four main functions; namely - Research (to research and develop a general policy towards privacy), Complaints, Public Education, and Law Reform.

#### 6.2.2 Health Commission of New South Wales

The Health Commission of N.S.W. refers any requests for research involving difficult confidentiality issues to the N.S.W. Privacy Committee, and is usually guided by that Committee's decision, before allowing the researcher access to Hospital Medical Records.

The Health Commission of New South Wales has also distributed a Circular No. 80/106, issued 31st March 1980, to all Hospitals and Community Health Centres.

Section 5 of this circular states "No information concerning a patient or client is to be supplied to another person without the written consent of the patient or client. This written consent must be preserved in the case notes". The client must be INFORMED of the purposes of the body requesting his confidential information, and must be legally capable of giving consent. This consent must be freely given, and cover what is required.

Section 8.3 states "Information should not be supplied for research without consent of the patient or consultation with the appropriate hospital or regional authority. Attention is drawn to the guidelines for access to data produced by the Privacy Committee".

6.2.3. Action being taken

Letters explaining the aims, requirements and methodology of the Veterans Herbicide Study will be sent to both the Privacy Committee of N.S.W. and the Health Commission of N.S.W., and if required, discussions will be organised between members of the Herbicide Study Group and the Privacy Committee. Prof. L. Davidson will be writing to the Department of Veterans' Affairs in Canberra to address the question of confidentiality of a national level.

At no time will medical records of any kind be viewed by a member of the Veterans Herbicide Study without the express informed consent of Veterans/Controls/Wives etc. Production of the patient's signed consent will accompany all requests for medical record validation.

Confidentiality and privacy of questionnaires will be maintained at all times within the offices of the Herbicide Study Group.

# 7. STATISTICAL ANALYSIS OF THE PILOT STUDY

## 7.1 Response Rates

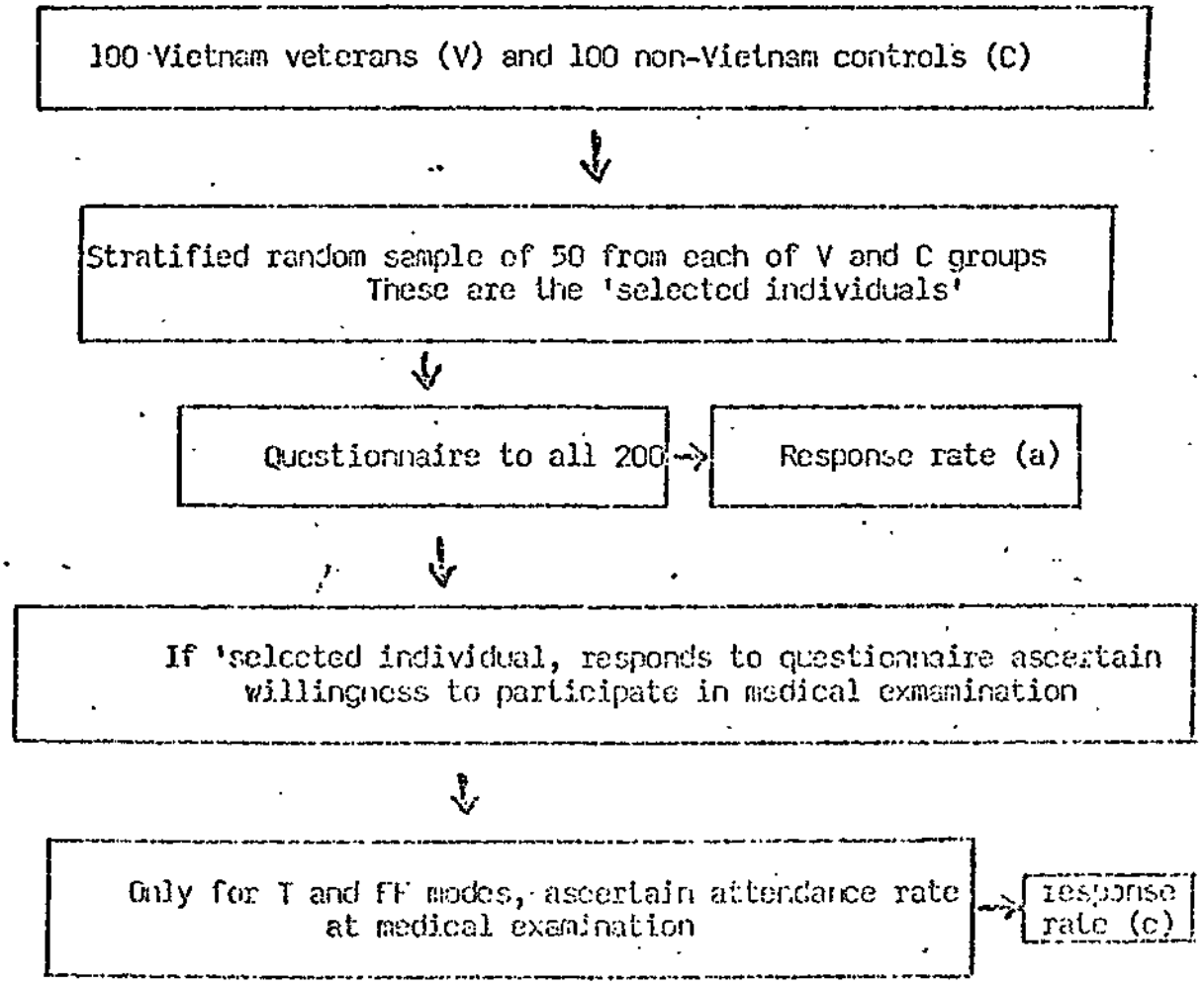
Three types of response rates are of interest:

(a) overall response i.e. whether any questions answered (? agreement to participate)

(b) internal response i.e. how many and which questions were answered satisfactorily. (This is an aspect of data quality)

(c) medical examination response i.e. how many of the respondents agree to and attend a medical examination

The rates (a) and (c) will be assessed as follows for each of the three interview modes:



Siemiatycki* has found that the three interview modes yielded response rates of

(a) SA - 70.3% (b) T - 73.5% (c) FF - 84.1%

Similar results are expected in our study and will be presented as follows:

| Interview Mode | Pecentage overall response | Within respondents % positive response to medical | Within respondents % attendance at medical |
|---|---|---|---|
| SA | | | (estimate only) |
| T | | | |
| FF | | | |

The estimate of the % attendance at medical for the SA mode will be calculated on the basis of the observed mean attendance rate among those in the T and FF modes who gave a positive response. Only an estimate is to be calculated for the SA mode because of the time requirements for the pilot survey. All response rates will be calculated using appropriately weighted values from each stratum.

The rate (b) will be used to identify sensitive areas of the questionnaire whose wording should be reconsidered and to alert the statistician to tests whose power may be seriously affected by the presence of missing values. Power studies will have to be conducted in the light of the (b) response rates.

All three response rates will be used as estimates of the figures to be expected in the main survey power calculations associated with the various hypotheses to be tested can then be made using these estimates.

7.2 Quality of data

There are two important aspects here:

(a) the problem of non-response on specific questions should be addressed. This has two obvious implications -

(i) can the question be changed so as to increase response rate?

(ii) what is the effect on the power of the tests to be carried out using, say, estimates of the missing values?

(*) J. Siemiatycki. A comparison of mail, telephone and home interview strategies for household health surveys AJPH 69: 238-245, 1979.

(b) The problem of bias i.e. false reporting of medical status. There are several ways in which one can try to detect this and determine how often it occurs in different types of individuals:

(i) use of medical records librarian to check on diagnosed illnesses

(ii) use Army entrance medical examination data if feasible on some reported illnesses

(iii) use incidence of medical disorders thought to be unrelated to herbicide exposure to "flag" over-reporting

(iv) look at correlations between the battery scores on the questionnaire and on the medical. Low correlation could indicate false reporting and/or an inconsistent form of scoring in these two modes.

7.3 Comparability

The issue of comparability of the V and C groups has several aspects:

(a) Medical records of the entrance exam will be available on all 600 individuals. In addition, age at enlistment, length of service and Regular/National service status are already known for each individual.

(b) Additional information will only be available from respondents. It is therefore necessary to determine whether the respondent (R) and non-respondent (NR) sections of the V and C subgroups sampled are comparable. This will be done via

(i) entrance medical exam records, age of enlistment, length of service, Regular/National service status, place of residence

(ii) a mini-questionnaire to NR's. This will ask for education, occupation and any chronic medical problems in self or family.

If the R and NR sections of the sample of 600 are comparable on the basis of (i) and (ii) in both the V and C groups, no adjustment is necessary. If not, the differences should be ascertained and taken into account when preparing power calculations for the main study and devising possible statistical analyses.

(c) The R sections of the V and C subgroups will be compared via additional information on the questionnaire e.g. nationality, income, education, occupation, rural/urban status.

(d) Within the V subgroups of respondents it will also be necessary to compare those who went into the field with those who stayed on the bases.

If it is found that groups are not comparable, the differences should be ascertained and their known effects in the areas of interest should be studied closely. Whenever possible, an appropriate adjustment should be incorporated in the analysis.

# 8. APPENDICES

## 8.1 Structure of the Interview/Questionnaire

### A. MALE QUESTIONNAIRE (For Pilot Study)

1. Personnel information.

2. General information
   - 2.1 Nature of study itself
   - 2.2 Subjects participation
     - 2.2.1. Importance
     - 2.2.2. Voluntary
     - 2.2.3. Confidential
   - 2.3 Contacts for further information.

3. Instructions.
   - 3.1 How to fill in the questionnaire
   - 3.2 What to do with completed questionnaire
     - 3.2.1. Where to send it
     - 3.2.2. Date to send it by
   - 3.3 Contacts for help in filling in questionnaire

4. Subject identification
   - 4.1 Todays date
   - 4.2 Surname
   - 4.3 Given names
   - 4.4 Address in full
   - 4.5 Home phone number
   - 4.6 Work phone number
   - 4.7 Confidential survey number

5. Demographics
   - 5.1 Date of birth
   - 5.2 Type of place where lived while growing up
   - 5.3 Years of schooling
   - 5.4 Tertiary qualifications
   - 5.5 Racial origins

6. Occupational and Exposure History
   - 6.1 General job history
     - 6.1.1. Prior to going defence services
     - 6.1.2 While in defence services
     - 6.1.3. After leaving defence services
   - 6.2 Job contact with specific chemicals and substances
   - 6.3 Absenteeism
   - 6.4 Details of defence service
     - 6.4.1 Date of enlistment
     - 6.4.2 Date of discharge
     - 6.4.3 Status within service
   - 6.5 Vietnam service
     - 6.5.1 Details of service
     - 6.5.2 Details of chemical exposures
       - 6.5.2.1 Spraying chemicals
       - 6.5.2.2 Mixing, carrying or loading chemicals
       - 6.5.2.3 Cleaning or repairing equipment used to carry chemicals

6.5.2.4 In area while it was being sprayed by aircraft
6.5.2.5 In area while it was being sprayed from vehicle, boat or backpack
6.5.2.6 In area where vegetation was dead and dying

6.6 Leisure time exposure to specific chemicals and substances

7. Medical history
   7.1 Height
   7.2 Weight
   7.3 Self-rating of health
      7.3.1 Physical health
      7.3.2 Mental health
   7.4 Specific medical conditions requiring validation
      7.4.1 Dermatologic
      7.4.2 Neoplastic
      7.4.3 Hepatic
      7.4.4 Haemopoietic
      7.4.5 Immunologic
      7.4.6 Cardiac
      7.4.7 Endocrine conditions
      7.4.8 Urinary/kidney conditions
      7.4.9 Reproductive
      7.4.10 Neurologic
      7.4.11 Psychological

8. History of smoking, alcohol and marijuana use
   8.1 Smoking history
      8.1.1 Now/ever
      8.1.2 Stopped/started
      8.1.3 Quantity
   8.2. Alcohol Consumption
      8.2.1 Now/ever
      8.2.2 Stopped/started
      8.2.3 Quantity

   8.3. Marijuana use
      8.3.1 Ever
      8.3.2 Quantity

9. Marital history
   9.1 Current marital status
   9.2 Number of marriages
   9.3 Number of relationships lasting more than 6 months

10. Pregnancy outcome
   10.1 Record of all live births
   10.2 Record of all occasions on which tried for a period of at least a year to conceive a child but were not able to do so
   10.3 Record of all pregnancies not ending in a live birth
   10.4 Record of all children born with birth defects
   10.5 Record of all children diagnosed as being cancer

11. Perceptions of husbands or ex-husbands health
   11.1 Physical health
   11.2 Mental health

12. Closing statment
    12.1 Thanks
    12.2 Reminder about what to do with questionnaire

## B. FEMALE QUESTIONNAIRE

1. Personnel information

2. General information
    2.1 Nature of study itself
    2.2 Subjects participation
        2.2.1 Importance
        2.2.2 Voluntary
        2.2.3 Confidential
    2.3 Contacts for further information

3. Instructions
    3.1 How to fill in the questionnaire
    3.2 What to do with completed questionnaire
        3.2.1 Where to send it
        3.2.2 Date to send it by
    3.3 Contacts for help in filling in questionnaire

4. Subject identification
    4.1 Todays date
    4.2 Surname
    4.3 Given names
    4.4 Address in full
    4.5 Home phone number
    4.6 Work phone number

5. Demographics
    5.1 Date of birth
    5.2 Years of schooling
    5.3 Tertiary qualifications
    5.4 Racial origins

6. Occupational History
    6.1 General job history

7. Medical history
    7.1 Height
    7.2 Weight

8. History of smoking and alcohol consumption
    8.1 Smoking history
        8.1.1 Now/ever
        8.1.2 Stopped/started
        8.1.3 Quantity
    8.2 Alcohol consumption
        8.2.1 Now/ever
        8.2.2 Stopped/started
        8.2.3 Quantity

9. Marital history
   9.1 Current marital status

10. Pregnancy outcome
   10.1 Record of all live births including children who have since died
   10.2 Record of all occasions on which tried for a period of at least a year to conceive a child but were not able to do so
   10.3 Record of all pregnancies not ending in a live birth
   10.4 Record of all children born with birth defects
   10.5 Record of all children diagnosed as having cancer

11. Perceptions of husbands or ex-husbands health
   11.1 Physical health
   11.2 Mental health

12. Closing statement
   12.1 Thanks
   12.2 Reminder about what to do with questionnaire

## 8.2 Structure of the Medical History and Medical Examination of Adults

It is proposed to examine 200 subjects and their children.

The time of the medical examination will be approximately 3 to 4 hours.

It is proposed to examine the veterans children at the same time generally in the company of their mother.

PROGRAMME

The proposed medical examination will be in six parts:- Administration, medical history, laboratory data collection, physical examination, psychological tests, examination of offspring.

SCOPE AND CONTENT OF THE MEDICAL EXAMINATION

1. ADMINISTRATION - 10 minutes.
   During administration identification details and age etc. will be collected

2. MEDICAL HISTORY - 45 minutes.
   Performed by Physician No. 1.
   The system review will be a standard medical history with more or less emphasis on outcomes of interest.

3. LABORATORY DATA - 15 minutes.
   Vene puncture to be performed by a nurse.
   Laboratory data to provide haematology and biochemical information.
   - Provision to be made for serum storage at $-70^{\circ}$ C.
   The nurse will also record vital statistics e.g. height, weight and supervise spirometry.

4. PHYSICAL EXAMINATION - 60 minutes.
   Performed by Physician No. 2.

   (i) General examination major systems.

   (ii) Skin examination with photography if necessary.

   (iii) Neurological examination.

   (iv) Examination of target organs e.g. liver, spleen, lymph glands and testes.

5. PSYCHOLOGICAL TESTS - 60 minutes.

   Proposed Psychological tests are the Cornell Index (C.I.) and the Minnesota Multiphasic Personality Inventory (MMPI).
   Two other indices that may be suitable are being considered - the Orme questionnaire and the Beck Depression Inventory. A re-run of the Army's psychological tests prior to entry into the services is being considered.

   These tests may be administered by a nurse.

6. OFFSPRING
- examination to be performed by a Paediatrician.

(i) General physical examination.

(ii) Birth defects.

## 8.3 Medical Examination of Children

As previously stated it is intended that the children of veterans be examined by a Paediatrician at the same time as the subjects are being examined.

Resources are being planned on the basis of examining approximately 400 children.

The medical examination of the children will have as its objectives:

1. An estimate of present state of health.
2. Recording of any observable birth defects
3. validation of any reported birth defects or medical conditions.

A provisional list of birth defects has been compiled based on the birth defects to be included in a case-control study of the effect of service in Vietnam to be conducted by the Center for Disease Control, Atlanta, USA.

A parent of the children will be asked about the listed birth defects and confirmation will be sought either with evidence of surgical correction or at physical examination.

Where the terminology is general and a positive response is obtained, specification and confirmation will be obtained via hospital and doctor medical records.

## 8.3.1. List of Birth Defects

SPINA BIFIDA AND/OR HYDROCEPHALUS
MICROCEPHALUS
NEUROFIBROMOTOSIS
ANOPHTHALMOS
MICROPHTHALMOS
BUPHTHALMOS
CONGENITAL CATARACT
COLOBOMA
ANOMALY OF THE EAR - IMPAIRING HEARING
HEART CONDITIONS
CONGENITAL CYSTIC DISEASE OF ANY ORGAN
ANOMALIES OF THE GASTRO INTESTINAL TRACT
CLEFT LIP AND/OR PALATE
HYPOSPADIUS
EPIDSPADIUS
ANOMALIES OF THE URINARY TRACT
ANOMALIES OF THE FEMALE GENITAL TRACT
CLUB FOOT
REDUCTION DEFORMITIES OF THE LIMBS
CHONDRODYSTROPHY
OSTEO GENESIS IMPERFECTA
HEREDITARY OEDEMA OF THE LEGS
SPECIFIC ANOMALIES OF HAIR
SPECIFIC ANOMALIES OF NAILS
ANOMALIES OF THE ENDOCRINE SYSTEM
SITUS INVERSUS
DOWNS SYNDROME
DIAPHRAGMATIC HERNIA
CONGENITAL NEOPLASM
CYOTOMEGALO VIRUS
HERPES SIMPLEX
SYPHYLIS

SECTION 2

DRAFT REPORT - 26/02/81

# HERBICIDE EXPOSURE IN VIETNAM

## CONSIDERATIONS

JOHN ROGERS

TABLE OF CONTENTS

## INTRODUCTION*

Research on 2,4-D, 2,4,5-T and related herbicides began during World War II, and had at that time a clearly military connotation. However, herbicides were not used for military purposes in World War II. The first, small-scale military use of herbicides was in the 1950's in the Malayan "emergency". In the early 1960's the possibility of tactical use of herbicides was given considerable impetus. A number of herbicides were evaluated, in various combinations, for their phytoxic effectiveness in South Vietnam.

In South Vietnam, the first military herbicide operations were carried out in early 1962, and were phased out in 1971. After a relatively slow buildup from 1962 to 1965, the operations increased rapidly to a peak in 1967, declined, but only slightly, in 1968 and 1969, and dropped sharply in 1970. According to information from US Department of Defence, the last herbicide spraying by fixed-wing aircraft was flown on January 7, 1971. After this, herbicide operations were limited to spraying around perimeters of the fire bases, on enemy cache sites, and along land and water communication routes, and were all carried out by helicopter or on the ground. The last helicopter operation under U.S. control was flown on October 31, 1971.

### Herbicides used by US forces

The herbicidal "Agents" used for military purposes in South Vietnam were identified by code names referring to the color of bands painted on the containers of the chemicals. Those of interest to this study are the Agents: Orange, White & Blue.

Agent Orange is a 50:50 mixture of the n-butyl esters of 2,4-D ([2,4-dichlorophenoxy]acetic acid) and 2,4,5-T ([2,4,5-trichlorophenoxy]acetic acid). Each gallon of Orange contained 4 lb of 2,4-D and 4.6 lb of 2,5,5-T on an acid equivalent basis.[a] Orange was the agent used most extensively in the Vietnam war until its use was terminated on April 15, 1970 because of the concerns of its possible teratogenicity and its contamination with the highly toxic TCDD (2,3,7,8-tetrachlorodibenzo-para-dioxin).

Agent White is a mixture containing 2 lb of 2,4-D and 0.54 lb of picloram (4-amino-3,5,6-trichloropicolinic acid) per gallon on an acid equivalent basis. (or 4:1 on a molar basis). It is a formulated product containing 2,4-D and picloram as the triisopropanolamine salts, with the addition of surfactants and water.

*This introduction is based on material in reference (17).

a Acid equivalent is the weight of the acid form of the chemical. this is used because the weights of various ester or amine formulations vary. Expression in terms of acid equivalents provides a uniform basis for comparison of different formulations.

Agent Blue was formulated as the sodium salt of cacodylic acid (hydroxydimethylarsine oxide). It contained a minimum of 21 percent sodium cacodylate with additional free cacodylic acid for a total dimethylarsinic acid equivalent of not less than 26 percent on a weight basis, or 3.1 lb of cacodylic acid and about 1.7 lb arsenic per gallon, with 5 percent surfactant and 0.5 percent antifoam agent.

All agents were intended for use at a rate of 3 gal./acre (28 litres per hectare), except that in the earlier operations and on rare occasions thereafter, only half of this dose was used. The herbicides were applied by US forces fixed-wing aircraft (UC-123), helicopter (UH-1), from trucks, from river boats, and from backpacks. South Vietnamese forces may have also been involved disseminating the herbicides Orange, White & Blue by these methods.

Both aircraft types were outfitted with special spraying equipment, consisting essentially of a container for the herbicide and a spray boom with nozzles. The container of the UC-123 spray system had a nominal capacity of 1000 gal. and the plane normally flew at 150 ft. (45 m) with a delivery speed of 130 to 140 knots. The "spray-on" time of 3 1/2 to 4 minutes permitted approximately 950 gallons of herbicide to be distributed at the rate of 28 litre/hectare over a path of 14 km length. During the peak of activity (1968-1969) approximately 30 C-123/UC-124 aircraft were employed. However, many other squadrons of C-123 aircraft were used routinely throughout South Vietnam in transport operations (4).

The capacity of the UH-1 spray system container was 200 gal. but the helicopter could carry only 100 gal. due to weight limitations. Spraying by fixed-wing aircraft accounted for the greater majority of the herbicide used in the Vietnam war, at least into the later part of 1970 from which time on helicopter herbicide operations increased and gradually became predominant, until they became the only aerial means of herbicide delivery. (17)

The amount of herbicide used by year is listed in table 1 (17) and the estimates of quantities of herbicide component total usage is given in table 2 (66). The region that received the greatest concentration of herbicides was the Rung-Sat Special Region south of Saigon and adjoining Phouc Tuy province (where the Australians were posted). This level is reflected in the quantities used in military region III which included the Rung-Sat Special Region (table 3). The correspondence of spray missions in military region III and the positions of Australian soldiers has yet to be determined - and the numbers involved is subject only to conjecture.

Table 1
Application of Herbicides in the Vietnam War by Year (17)

| | Millions of Gallons | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | 1962-July 1965 | Aug-Dec 1965 | 1966 | 1967 | 1968 | 1969 | 1970 | 1971 | Total |
| Orange | NA[a] | .37 | 1.64 | 3.17 | 2.22 | 3.25 | .57 | .00 | 11.22 |
| White | NA[a] | 0 | .53 | 1.33 | 2.13 | 1.02 | .22 | .01 | 5.24 |
| Blue | NA[a] | 0 | .02 | .38 | .28 | .26 | .18 | .00 | 1.12 |
| Total | 1.27 | .37 | 2.19 | 4.88 | 4.63 | 4.53 | .97 | .01 | 18.85 |

a Not available

TABLE 2. Estimated quantities of herbicides and TCDD disseminated in South Vietnam from January 1962-February 1971 (65)

| Chemical | Pounds |
|---|---|
| 2,4-D | 55,940,150 |
| 2,4,5-T | 44,232,600 |
| TCDD[a] | 368 |
| Picloram | 3,041,800 |
| Cacodylic Acid | 3,548,710 |
| Total of Herbicides | 106,763,260 |

a The mean TCDD concentration in Herbicide Orange was estimated at 1.98 ppm.

TABLE 3 US Herbicides Expenditures in South Vietnam, 1962-1971: A Breakdown by Combat Tactical Zone *

| Combat Tactical Zones | Herbicide Expenditure (gallons) Orange | White | Blue |
|---|---|---|---|
| CTZ I | 2,250,000 | 363,000 | 298,000 |
| CTZ II | 2,519,000 | 729,000 | 473,000 |
| CTZ III (includes Saigon) | 5,309,000 | 3,719,000 | 294,000 |
| CTZ IV | 1,227,000 | 435,000 | 62,000 |
| Subtotals | 1,227,00 | 5,246,000 | 1,127,000 |
| Grand total | | | 17,678,000 |

* Source: HERBS tape (65)

Herbicides used by Australian forces

Australian troops may have also been exposed to herbicides sprayed for perimeter vegetation control around the Australian camps. The chemicals used were on the whole obtained commercially from within Australia and included GRAMOXONE (paraquat) REGLONE (diquat), TORDON 50D (picloram/2,4-D) and HYVAR (bromacil). The annual usage in Vietnam in the years 1968 to 1971 was of the order of (6):

9,000 liters of diquat
1,600 liters of TORDON 50D
4,000 kg bromacil

Commencing November 1967 a field investigation was conducted under scientific supervision to establish the methodology for disseminating these herbicides. Subsequent to toxic effects being found in operators - breakdown of mucous membranes, nose bleeds, ulceration of lips and conjunctivitis - the use of DMSO* was discontinued and strict procedures for handling were recommended (31).

In addition the Department of Defense "accords a fairly high degree of probability" that the Australia Task Force procurred and used 1,000 gallons of Agent Blue (cacodylic acid) obtained from local sources (6).

* DMSO is a chemical which accelerates the uptake of herbicide into plants, and unfortunately has the same effect for humans.

Non Herbicide Exposures

Further to the herbicides disseminated by the U.S. forces, the Australian troops may have come in contact with Malathion sprayed from specially prepared C-123 planes or "bug-birds". The Malathion was selected for malarial mosquito control on advice from the World Health Organization. Unlike the herbicides which were sprayed in "remote" areas the Malathion was sprayed "indiscriminately" over populated areas, "even whole towns" (A.L. Young, private communication). These aircraft routinely sprayed insecticide adjacent to military and civilian installations, as well as in areas where military operations were in progress or about to commence (4)

Medical treatments are also of interest, in particular (1) antimalarial drugs including the experimental drug Dapsone which was used between 1969 and 1970 and withdrawn after adverse side effects and (2) innoculations for Plague which too had adverse side effects but remained in use.

Summary of possible chemical exposures in Vietnam

Thus the chemicals which are of interest to the Australian Veterans Herbicide study are:

1. Agents used by U.S. forces
   (a) Orange
   (b) White
   (c) Blue
   (d) Malathion;

2. "Agents" used by Australian forces
   (a) Grammoxone
   (b) Reglone
   (c) Hyvar
   [(d) Agent Blue]
   (e) Insecticides;

3. Australian Medical Treatments
   (a) Antimalarials
   (b) Plague innoculations.

Modelling exposure

The object of the Veterans Herbicide Study is to explore the causal effects of herbicide exposure in Vietnam with regard to possible adverse health outcome in Australian Vietnam Veterans.

The hypothesis that a certain herbicide (or even combinations of chemicals) could cause the undesirable health effect can only be demonstrated by being consistent with the current knowledge of the chemical(s) biological action. Secondly to validate the supposition a dose-response relationship must be shown i.e. The health effect should increase with increasing exposure.

Any attempt to determine the 'dose' or exposure of military personnel must be predicted on events that occurred at least ten years ago. Since there was no sampling program associated with the handling or dissemination of the herbicides in South Vietnam, a quantitative determination of exposure in terms of actual dose can only be subject to speculation (4). However, it is still possible to determine "relative" exposure levels.

For the "Agents" of greatest concern, namely Orange, White and Blue, it is true to say that exposure did not include all Australian servicemen. Moreover, within the military population at risk, the range in magnitude of exposure must have been great. The range is so great that it is plausible that the possible errors in predicting this "relative" exposure may be less than the range itself.

Data

To predict exposure levels with certainty it is necessary to have a minimum of verifiable data available. To demonstrate a possible causal or 'legal' connection requires a higher standard of documented information.

Exposure to Malathion is a case which amplifies this point. No documented information regarding the "indiscriminate" spraying of this substance is available. It may be possible to show relationship between other highly correlated confounding factors, such as combat duty or season and presumed Malathion exposure. Without supplementary documentary evidence it is impossible to separate the effects of the selection criteria from the exposure.

A correlation between such "Malathion exposure" and health effects would be insufficient to prove the causal nature of exposure. There is no way that such an effect could be ascribed to the exposure to Malathion alone.

To obtain a presumed exposure level for Agents Orange, White and Blue the following sources of data are available:

1. The so called "HERBS" computer tapes which document the herbicide spraying missions of United States fixed wing aircraft. [approximately 80% of total herbicide disseminated by

United States and South Vietnam forces is documented on these tapes]. The information on tape includes: Start co-ordinates, finish co-ordinate, gallons of agent and type of agent. The spraying from helicopters is omitted - as is record of aerial spraying before 1965.

2. The Australian army has supplied the locations of approximately 70% of Australian Units [based on commander diary information]. This is the so called "CARO" data. Vital co-ordinate information is currently incomplete, but should be able to be obtained.

3. A comprehensive survey of all Army personnel in South Vietnam to be conducted by this study will include questions to fill in information gaps i.e. Report possible exposure to helicopter spray missions; unit postings (which are not included in "CARO" data); subjective information on exposure to handling herbicides, spraying from backpacks, trucks and boats, to aerial spraying and to areas that were recently sprayed. Questions allowing the assessment of the internal consistency of the sources of information are to be included.

4. Survey questions will include checks for accidental and occupational exposure to phenoxy herbicides, arsenicals, asbestos and other detrimental environmental agents outside the potential exposure in Vietnam.

Aerial Spraying

The exposure to the aerial application to these agents may be separated logically into four areas:

a. Spray drift and concentrations in "jungle"* from aerial application. This concerns the fate of spray from the time the spray leaves the plane until spray particles impact on the jungle foliage, tree trunks and ground and to the herbicide distribution within the jungle ecosystem.

b. Environmental fate in jungle and hence likely sources of contamination. Addresses the following areas:

   i) volatalisation and revolatalisation

   ii) photodecomposition and biodegredation of herbicide components

   iii) redistribution of herbicide components within the jungle environment e.g. after leaf fall

   iv) Bioaccumulation

* "jungle" is used to indicate all possible types of vegetation such as forest, savanna, mangrove, swamp and cultivated land.

c. Exposure modes:

i.e. exposure via dermal, alimentary and pulmonary routes including relative absorption values and likely sources of contamination via each route.

d. Exposure categories

i.e. use current data in the scientific literature to choose a priori meaningful exposure level categorisations.

a) Spray drift

There are two models which are proposed for spray drift calculation. They are not of necessity mutually exclusive and are as follows:

i) "Deterministic" model of spray fate.
"The generalised model format is for a mass continuity equation that in principle provides a complete description of the trajectory and properties of an aerosol or heavy particulate cloud, from the time of cloud stabilization to the collection by downwind surfaces. The terms included in the generalised model must therefore specify the direction and rate of downwind cloud travel, the alongwind crosswind and vertical cloud dimensions of travel time and distance, the distribution of material within the cloud as a function of time and distance, and loss of material through gravitational settling, impaction or deposition on vegetation or other surfaces." (19) The model should also provide for the effects of variations in chemical and physical properties of the material contained in the spray cloud e.g. the volatility of components; the mode of release and source emission time; and in meteorological, micro-meteorological, terrain and vegetative factors.

Spray "drift" is used interchangably to describe two distinct processes. The first type of "drift" refers to the variation of the actual flightpath to the "HERBS" data and the second to the spreading of the spray cloud due to physical and meteorological conditions. The former could conceivably be tens of kilometres while the latter should be 1 kilometre at most.

Although it has been stressed that the pilots were able to lay spray swaths accurately and that drift "just did not occur" (A.L. Young private communication), [Herbicide]" mission commanders stated that drift was a common problem and could extend from 1 to 2 kilometers. One "Ranch Hand" commander said in several cases drift could be up to 10 km. (These instances were mountainous regions usually occupied by enemy forces) (18).

To reliably estimate the spray fate requires the following information.

1) Actual flightpath. The "HERBS" tapes give the positions of flightpath endpoints. Since all the fixed wing mission

preparation included aerial reconnaisance it may be assumed that the endpoints or at least the startpoint was reliably achieved. However it has been stated that the actual flightpath may have deviated markedly from a straight line (A.L. Young private communications) with terrain being a major factor. Furthermore, if a mission involved clearing jungle along a river bank or road, the straight line approximation would be grossly in error*.

2) Spray particle size distribution is a critical factor in determining drift potential, revolatilisation and particularly fate within the jungle canopy - drops smaller than 150um would pose a problem. If the spray is volatile, i.e. Orange, the larger droplets can vapourise to these dimensions, exaggerating the problem. The droplet size is highly dependent on viscosity, nozzle geometry, spray system pressure and aircraft speed. Incomplete data on particle size distribution is included in Table 4.

TABLE 4 Spray characteristics of C-123 Modular Internal Spray System. (4) (Spray material unknown)

| | |
|---|---|
| Aircraft speed | 130 Knots |
| Aircraft altitude | 150 ft (45 m) |
| Tank volume | 1,000 gal (4,500 l) |
| Spray time | 3.5-4 min |
| Particle size: (percentage by volume) | |
| 100u 1.9% | |
| 100-500u 76.2% | |
| 500 21.9% | |
| 87% impacted within 1 min | |
| 13% drifted or volatilized | |
| Mean particle volume | 0.6lul |

* The committee on Effects of Herbicides in Vietnam (17) found several instances where defoliation missions were more than 8km from the nominated path.

The problem of volatility would also affect the water soluble Agents Blue and White which were sprayed in a concentrated form. Experience in agriculture has shown that it is possible for the water to vapourise from spray particles leaving a dust of the concentrate which impacts with extreme unreliability (70). The effect varies inversely with droplet size. The water solubility of these Agents mean that they have a vastly different environmental fate if it rained within 6 hours of application.

3) Micro-meterology. The deposition and/or drift of a spray cloud is highly dependent on the local meterological conditions. Such factor as terrain, jungle surface and time of day dictate local wind direction, thermals and inversions which are impressed upon the larger scale weather patterns. Fortunately jungle provides micrometerological patterns which are stable over large areas so reliable predictions are possible given the factors of terrain, jungle surface, time of day and weather.

A factor which interacts considerably with micro-meteorological factors to produce drift is aircraft spray height - it must be stressed that, although highly dedicated, the US pilots were operating under combat conditions, in many cases over difficult terrain so that the value of 150ft (45m) must be treated as a nominal altitude only.

## Conclusions

The overwhelming problem yet to be faced is that of the validity of this model. Agricultural experience (70) has shown the inadequacies, even disasters, of models of spray behaviour in well controlled situations. The variety of specialised models available and the controversy over their validity (8), (9), (19), (70), (71) illustrates the potential problems.

Furthermore the available models concern the application of dilute solutions (of the order of 1 in 100) applied over an even crop surface by single light plane from an altitude of 3 meters versus the situation in Vietnam where a concentrated solution was applied over a rough jungle surface by a formation of cargo planes, flying at a nominal 45 meters. The utility of such models to the Vietnam situation could only be classed as fortuitous.

In addition volatile esters "were requested [and used] in order to achieve more uniform coverage within a forest canopy"(66). Thus the volatalisation from particles within the spray cloud and from herbicide on leaf surfaces must be included in any model of spray fate and/or exposure.

It is obvious that there are many problems to be addressed before the deterministic model would be a viable proposition. Validity could only be assessed by a careful re-enactment of the Vietnamese spraying operations under a variety of operational and weather conditions.

ii) Statistical Model

The requirements of the "deterministic" model for hard data may not be fulfilled from the distance of time so it is suggested that a simpler "statistical" model of spray fate be used.

It will be assumed that the planes started from the "HERBS" startpoint and headed in the direction of the endpoint. The variance of the probability distribution function of the actual flightpath is assumed to increase with increasing distance from the startpoint. The "actual" endpoint is distributed at a mean distance of 14 km from the startpoint.

The percolation and vertical distribution of spray within the jungle is more complex. The "deterministic" model would be of great benefit in calculating this distribution. The most satisfactory method would be to assign various fractions of the spray cloud to the sections of interest in the jungle ecosystem i.e. soil and lower canopy.

The spray swath distribution function is derived assuming the flightpath is known. The major factor affecting variance of this distribution function being the number of aircraft and the terrain.

The position of the troops will be treated as a two dimensional gaussian distribution centered on the "CARO" data co-ordinate. The variance will include such factors as co-ordinate accuracy and whether the troops were on patrol.

The time effect is included in a simple exponential model of herbicide component decay choosing appropriate decay rates from the scientific literature. The effect of vegetation cover protection and exposure modes is included as a multiplicative factor. Considering the simplifications so far, it is proposed that a simple cumulative model of exposure be used, giving relative exposure days as an output. (For the full mathematical treatment see Appendix III.)

Comments

The relativity of unrelated modes of exposure poses scientific problems which will take at least 6 man months to treat. References (5), (22), (26), (40), (41), (42), (50), (58) and experience in Australia with council workers spraying 2,4,5-T coupled with U.S. Air Force documents (currently requested) concerning calibration and spray simulation will enable a reasonable connection to be obtained.

The latter documents will also provide a more accurate basis for the numerical values proposed in Appendix III.

The work of Isensee (36) has shown that bioaccumulation (1000-6000 x accumulation) of dioxin contained in contaminated silt is possible by aquatic organisms. Considering the volume of Agent Orange (the source of dioxin) which was distributed over the Rung Sat

fishing region it is highly probable that seafood was a source of dioxin contamination - the relative amounts and significance is highly speculative. For the purposes of regression analysis on health effects it is hoped that this background exposure is no a significant fraction of the total exposure.

Recommendations

1. Run modified "HOPPS" program using simple assumptions to estimate size of exposed group.

2. Maintain liason with Australian and U.S. experts in the fields of Pesticides.

3. Continue collecting relevant articles from World literature.

4. Develop models for
   (a) Spray drift
   (b) Environmental fate of herbicides
   (c) Exposure modes
   (d) Exposure categories.

5. That the models of drift and environmental fate be tested using simulants to assess likely validity of theoretical predictions of drift and foliage penetration under conditions similar to those in South Vietnam.

6. The proposed models should be subject to extensive scientific peer review

## REFERENCES


1. Comments by Dow Chemical Company on presentation made by Dr. T.D. Sterling Royal Commission - Herbicides and Pesticides Vancouver 1974 1975

2. Report of the Consultative Council on congenital abnormalities in the Yarram District Dept. of Primary Industry Canberra 1978

3. Principles and Methods for evaluating the toxicity of chemicals. Part 1 Environmental Health Criteria 6 WHO 1978

4. Criteria for Determining Exposure Levels of Military Personnel to Dioxin and Herbicide Orange during the Vietnam War (draft) USAF 1980

5. Advisory Committee on Pesticides Further Review of the Safety for use in the U.K. of the Herbicide 2,4,5,-T - 1980

6. Pesticides used in Vietnam Hostilities and their use in Australian Agriculture: Comparitive Study (draft) Environmental Health (Aust. Dept. Health) 1980

7. Anon Report on the Aerial use of Phenoxy Herbicides Department of Food and Agriculture California 1978

8. Bache D.H., Sayer W.J.D. Transport of Aerial Spray, I. A model of Aerial Dispersion Agric. Meterol. 15 pp 257-271 1975

9. Bache D.H., Uk S. Transport of Aerial Spray, II. Transport within a crop canopy Agric. Meterol. 15 pp 371-377 1975

10. Barnes J.M. Assessing Hazards from prolonged and repeated exposure to low doses of toxic substances Br. Med. Bull. 31 pp 196-200 1975

11. Bartleson F.D., Harrison D.D., Morgan J.D. Field Studies of wildlife exposed to TCDD contaminated Soils AFATL-TR-75-49 1975

12. Baur J.R., Bovey R.W., McCall H.G. Thermal and Ultraviolet loss of Herbicides Arch. Environ. Contam. Toxicol 1 pp 289-302 1973

13. Böhm H.H., Müller H. Model Studies on the Accumulation of Herbicides by Microalgae Naturwissensnaften 63 p296 1976

14. Bovey R.W., Young A.L. The Science of 2,4,5,-T and Associated Phenoxy Herbicides Wiley 1980

15. Byast T.H., Hance R.J. Degredation of 2,4,5,-T by South Vietnamese Soils incubated in the Laboratory - 197?

16. Cocucci S. et al Absorption and Translocation of tetrachlorodibenzo-p dioxin by plants from polluted soil Experientia 35 pp482-484 1979

17. Committee on the Effects of Herbicides in Vietnam The Effects of Herbicides in South Vietnam Part A - Summary and Conclusions National Academy of Sciences 1974

18. Comptroller General U.S. Ground Troops in South Vietnam were in areas sprayed with Herbicide Orange U.S. General Accounting Office 1979

19. Cramer H.E., Boyle D.G. The Micrometeorology and physics of spray particle behaviour - -

20. Crosby D.G. Conquering the Monster -- The Photochemical Destruction of Chlorodioxins 174th National Meeting of American Chemical Society 1977 (See Report on Aerial use ...)

21. Crosby D.G., Wong A.S. Environmental Degredation of 2,3,7,8-Tetrachlorodibenzo-p-dioxin (TCDD) Science 195 pp 1337-1338 1977

22. Dhar M.M., Tandon J.S., Sircar K.P. Absorption and Excretion of 2,4,5-Trichlorophenoxy Acetic Acid in Man Arch. int. Pharmacodyn. 210 pp 250-255 1974

23. Dodge J.M. The Phenoxy Herbicides - A Summary - 1977

24. Donaldson T.W., Irvine F.N. 2,4,5-T Residues in Blackberry Fruit 7th Asian Weed Science Society Conf. 1979

25. Farwell S.O., Robinson E., Powell W.J., Adams D.F. Survey of airbourne 2,4-D in South Central Washington J. Air. Pollut. Contam. 26 pp 224-30 1976

26. Feldman R.J., Haibach H.L. Percutaneous Penetration of some Pesticides and Herbicides in Man Tox. Appl. Pharm. 28 pp 125-132 1974

27. Gebefügi I., Baumann R., Korte F. Photchemischer Abbau von 2,3,7,8 (TCDD) unter simulierten Umweltbedingungen Naturiwissenschaiften 64 pp 486-487 1977

28. Gehring P.J. et al The Fate of 2,4,5-T Following Oral Administration to Man Tox. Appl. Pharm. 26 pp 352-361 1973

29. Hance R.J. Herbicide persistence and breakdown in soil in the long term Proc. Assoc. App. Biol. -

30. Hiles R.A. and Bruce R.D. 2,3,7,8-Tetrachlorodibenzo-p-dioxin elimination in the rat: First order or zero order? Cosmet. Toxicol. 14 pp 599-600 1976

31. Holt E.S. (Major) A Report of the spraying of Herbicides at 1st Australian Task force, Vietnam A.A.O.R.G. Report 2/68 1968

32. Hook J.B., Cardona R. Osborn J.L., Baillie M.D. The Renal Handling of 2,4,5,-T in the Dog Cosmet. Toxicol. 14 pp 19-23 1976

33. IARC Monographs Vol. 2 Some inorganic and organometalic compounds IARC Lyon 1973

34. IARC Monographs Vol. 15 Some Fumigants, the Herbicides 2,4,-D and 2,4,5,-T, Chlorenated Dibenzodioxins and Miscellaneous Industrial Chemicals IARC Lyon 1977

35. IARC Monographs Vol. 23 Some Metals and Metallic Compounds IARC Lyon 1980

36. Isensee A.R. Bioaccumulation of 2,3,7,8 (TCDD) in 'Chlorinated Phenoxy Acids and their Dioxins' Ramel (ed) 1978

37. Isensee A.R., Jones G.E. Absorption and Translocation of Root and Foliage Applied 2,4-Dichlorophenol, 2.7 - Dichlorodibenzo-p-dioxin, and 2,3,7,8 TCDD J. Agr. Food Chem. 19 pp 1210-1214 1971

38. Kimbrough R.D. (ed) Halogenated Biphenyls, Naphthalenes, Dibenzodioxins and related products Elsevier North Holland 1980

39. Kirkwood R.D. Plant target areas and methods of attacking them Aerial Application of Pesticides 2 Cranfield 1980

40. Kolmodin-Hedman B, Erne K and Akerblom M. Field Application of phenoxy herbicides in Field Worker Exposure during Pesticide Application ed Tordoir 1979

41. Lavy T.L. Measurement of 2,4,5-T exposure of forest workers National Forest Products Associaton 1978

42. Leng M.L. Realistic Evaluation of Human Exposure from application of 2,4,5-T sprays Dow Chemical Company 1978

43. McNulty W.P. Toxicity of 2,3,7,8 - Tetrachlorodibenzo-p-dioxin for Rhesus Monkeys: Brief Report Bull. Environ. Contain Tox 18 pp 108-109 1977

44. Nash R.G., Beall M.L. Fate of Silvex, 2,4,-D and 2,3,7,8, TCDD in a microagroecosystem chamber ABS PAP AM. CHEM SOC. 175 p57 1978

45. Nash R.G., Beall M.L. Distribution of Silvex, 2,4,-D and TCDD Applied to Turf in Chambers and Field Plots J. Agric. Chem. 28 pp 514-623 1980

46. Office of the President Report on 2,4,5-T A report of the panel on Herbicides of the President's Science Advisory Committee. C.M. McLeod Chairman. Office of Science and Technology

47. Poland A., Glover E., Kende A.S. Stereospecific, High Affinity Binding of 2,3,7,8 - Tetrachlorodibenzo-p-dioxin by Hepatic Cytosol J. Biol Chem 251 pp 4936-4946 1976

48. Poland A., Kende A. 2,3,7.8-Tetrachlorodibenzo-p-dioxin: environmental contaminant and molecular probe Fed. Proc. 35 pp 2404-2411 1976

49. Poland A., Kende A. The Genetic Expression of AHH Activity: Evidence for receptor mutation in nonresponsive mice Origins of Human Cancer Cold Spring Harbor 1977

50. Ramsey J.C., Lavy T.L. and Braun W.H. Exposure of Forest Workers to 2,4,5-T: Calculated Dose Levels Dow Chemical Company 1979

51. Reggiani G. Estimation of the TCDD toxic potential in the light of the Seveso accident 20th Cong. E. Soc. Toxicol (Berlin) 1978

52. Rose J.Q. et al The Fate of 2,3,7,8 - Tetrachlorodibenzo-p-dioxin following single and repeated Oral Doses to the rat Tox. Appl. Pharm. 36 pp 209-226 1976

53. Schultz D.P., Harman P.D. Residues of 2,4,-D in Pond Waters, Mud, and Fish 1971 Pest. Mon. J. 9 pp 173-179 1974

54. Simpson G.R. Aerial Spraying - Safe Use of Pesticides on Cotton Crops Health Commission of N.S.W. 1979

55. Sirons G.J., Frank R.F., Dell R.M. Picloram Residues in Sprayed Macdonald Cartier Freeway Right of Way Bull Environ. Contam. Tox. 18 pp 526-533 1977

56. Stevens T.S., DiPasquale L.C., Farmer J.D. Acute Inhalation Toxicology of the Technical Grade Organoarsenical Herbicides, Cacodylic Acid and Disodium Methanearsonic Acid Bull. Environ. Contam. Tox. 21 pp 304-311 1979

57. Stewart W. A Retrospective Study of Agent Orange and Cancer Among Vietnam Veterans (Draft) US Veterans Association 1979

58. Tordoir W.F., Van Heemstra (ed) T. Field Worker Exposure during Pesticide Application Elsevier North Holland 1980

59. Torstensson N.T.L. Degredation of 2,4-D and MCPA in Soils of low pH Env. Qual. Safe. (Supp) 3 pp 262-5 1975

60. Walsh L.M. et al Occurrance and Distribution of Arsenic in Soils and Plants Environ. Health Pers. 19 pp 67-71 1977

61. Ward C.T., Matsumura F. Fate of 2,3,78 (TCDD) in a Model Aquatic Environment Arch. Environ. Contam. Tox. 7 pp 349-357 1978

62. Wauchope R.D., McWhorter C.G. Arsenic Residues in Soybean Seed From Simulated MSMA Spray Drift Bull. Environ. Contam. Tox. 17 pp 165-167 1977

63. Weakley B.S. How dangerous is sodium cacodylate? J. Micros. 109 pp 249-251 1977

64. Woolson E.A. Fate of Arsenicals in Different Environmental Substrates Environ. Health Pers. 19 pp 73-81. 1977

65. Young A.L. Use of Herbicides in South Vietnam 1961-1971 Educational Conference on Herbicide Orange, Silver Springs Maryland 1980

66. Young A.L., Calcagni J.A., Thalken C.E., Tremblay J.W. The Toxicology, Environmental Fate, and Human risk of Herbicide Orange and its associated Dioxin USAHL TR-78-92 1978

67. Young A.L., Thalken C.E., Arnold E.L., Cupello J.M., Cockerham L.G., Fate of 2,3,7,8 (TCDD) in the Environment: Summary and Decontamination Recommendations USAFA-TR-76-18 1976

68. Young A.L., Wolfe W.H. Criteria for estimating exposure levels of military personnel to Dioxin and herbicide Orange during the Vietnam War Position Paper submitted by US DOD to US VACC 12 Dec 1979

69. Zepp R.G., Wolfe N.L., Baughman G.L., Gordon J.A. Chemical and Photochemical Alteration of 2,4-D Esters in the Aquatic Environment Southeast Env. Res. Lab. U.S. E.P.A. 1975

70. Casimir M., Watt J.W. Aerial Spray Application Against Insects Pests AG Bulletin. Department of Agriculture NSW 1979

71. Cranfield Institute of Technology College of Aeronautics. Aerial Application of Pesticides. Vol. I-II, Short Course, 1980.

APPENDIX I.

Comments on Recommendations

2. (a) Mr James Watt, Research & Development Officer (Bayer Australia), 666-9841
   - field trials/aerial spraying (mathematical models/literature)

   (b) Mr Jack Snelson, Pesticides Co-ordinator for Commonwealth Department of Primary Industry (062) 72-3933
   - most complete source of world literature concerning pesticides available in Australia

   (c) Mr Brad Brett, Australian Veterinary Chemical Association (AVCA), 8th Floor, 60 York Street (290-0700)
   - good source of literature
   - excellent contacts in private and public sectors

   (d) Dr "Dick" Albanez
   - statistics
   - theoretical models of spray drift
   - exposure (of Ranch Hand personnel).

3. (a) Jack Snelson is an excellent source

   (b) C.I.H. library is most helpful in obtaining material once the reference is found

   (c) Commonwealth Health library, Canberra has access to the Dialog database which includes Chemical Abstracts and Science Citation Index. The latter is the most useful source for (i) obtaining complete list of material published by a given author in given years (ii) obtaining a complete list of all books/articles which cite a given work. Relevant authors are:

   Alan Poland - enzyme induction
   D.G. Crosby - herbicide degredation
   G. Reggiani - Seveso/dioxin long term effects.
   H.E. Cramer - Spray drift

   (d) The Medlars/Medline database has already been searched and printouts are filed. (This database is limited because it excludes articles without a direct medical context.)

   (e) Obtain as much information as possible concerning American experiences with their surveys via Dick Albanez and Bill Wolfe - especially information which Al Young may have, and the report by Steven Meeks dealing with the herbicide spray mission simulations done in Florida by USAF.

APPENDIX II

References yet to be obtained

Anonymous, 1974. Disposition of Orange Herbicide by incineration. Final Environmental Statement. Department of the Air Force, Washington, D.C. 737 p.

Bethel, J.S., Turnbull, K.J., Briggs, D. and Flores, J., 1975. Military defoliation of Vietnam forests. American Forests, 81(1):26-30, 56-61.

Brown, J.W., 1962. Vegetational spray tests in South Vietnam. U.S. Army Chemical Corps Biological Laboratories, Fort Detrick, Frederick, Maryland. 119 p. Available from the Defense Documentation Center, Defense Logistics Agency, Cameron Station, Alexandria, Virginia, DDC Number AD 476961.

Carrier, J.M., 1974. The location of herbicide missions and Hickey's Informants in South Vietnam. The Effects of Herbicides in South Vietnam. Part B. Working Papers. National Academy of Science, Washington, D.C. 15 p.

Coates, J.H., Sharpe, L.M. and Pollack, H., 1962. The present status of chemical control of vegetation in relation to military needs. Technical Notes 62-68. Institute for Defense Analyses, Department of Defense, Wasnington, D.C. 30 p.

Craig, D.A., 1975. Use of Herbicides in Southeast Asia. Historical Report. San Antonio Air Logistics Center, Directorate of Energy Management, Kelly AFB, Texas. 58 p.

Darrow, R.A., 1973. Foliage characteristics and defoliation/herbicidal responses in a Thailand Forest. Weed Sci. Soc. Am. Abstr. 66, pp. 29-30.

Darrow, R.A., Irish, K.R. and Minarik, C.E., 1969. Herbicides Used in Southeast Asia. Technical Report SAOQ-TR-69-11078. Directorate of Air Force Aerospace Fuels, Kelly AFB, Texas. 60 p.

Darrow, R.A., Trucheiut, G.B. and Bartlett, C.M., 1966. OCONUS defoliation test program. Technical Report 79. Crops Department,, Biological Sciences Laboratory, U.S. Army Biological Center, Fort Detrick, Frederick, Maryland. 216 p.

Demaree, K.D. and Creager, R.A., 1968. Defoliation tests in 1966 at Base Gagetown, New Brunswick, Canada. Technical Memorandum 141. Department of the Army, Fort Detrick, Frederick, Maryland.

Fee, D.C., Hughes, B.M., Taylor, M.L., Tiernan, T.O. and Hill, C.E., 1975. Analytical Methodology for Herbicide Orange. Vol. II. Determination of Origin of USAF Stocks. Technical Report ARL-75-0110. Aerospace Research Laboratories, Wright-Patterson AFB, Ohio. 30 p.

Grover R.J. Relative Velocities of ester & amine formulations of 2,4-D Weed Sci. 24: 26-28

Grover R.J., Maybank J. and Yoshida K. 1972 Droplet and vapour drift from butyl ester and dimethylamine salt of 2,4-D Weed Sci 20: 320-324

Harrigan, E.T., 1970. Calibration Test of the UC-123K/A/A45Y-1 Spray System. Technical Report ADTC-TR-70-56. Armament Development and Test Center, Eglin AFB, Florida. 160 p.

Hughes, B.M., Fee, D.C., Taylor, M.L., Tiernan, T.O., Hill, C.E. and Wu, R.L.C., 1975. Analytical Methodology for Herbicide Orange. Vol. I. Determination of Chemical Composition. Technical Report ARL-75-0110. Aerospace Research Laboratories, Wright-Patterson AFB, Ohio. 357 p.

Hurtt, W. and Darrow, R.A., 1968. Biological effectiveness of Stull Bifluid and Orange. Technical Report AFATL-TR-68-122. Air Force Armament Laboratory, Eglin AFB, Florida. 31 p.

Irish, K.R., Darrow, R.A. and Minarik, C.E., 1969. Information manual for vegetation control in Southeast Asia. Micl. Public. 33. Department of the Army, Fort Detrick, Frederick, Maryland. 71 p.

Kearney, P.C., Woolson, E.A., Isensee & Helling, C.S., 1973. Tetrachlorodibenzodioxin in the Environment: Sources, Fate and Decontamination. Environ. Health Perspect. Exp. Issue No. 5, pp. 273-277.

Klein, R.E. and Harrigan, E.T., 1969. Comparison Test of Defoliants. Technical Report ADTC-TR-69-30, Vol. I. Armament Development and Test Center, Eglin AFB, Florida. 356 p.

McConnell, A.F., 1970. Mission: RANCH HAND. Air University Review, 21(2):89-94.

Newton,, M., 1975. Environmental impact of "Agent Orange" used in reforestation tests in Western Oregon. Weed Sci. Soc. Am., Abstr. 144, 52 p.

Tschirley, F.H., 1968. Response of tropical and subtropical woody plants to chemical treatments. Research Report CR-13-67. Agricultural Research Services, U.S. Department of Agriculture, Washington, D.C. 197 p.

Westing, A.H., 1976. Ecological consequences of the second Indochina War. Stockholm International Peace Research Institute. Almgrist and Wiksel International, Stockholm, Sweden. 119 p.

APPENDIX III

Statistical model

To be tabled at meeting.

SECTION 3

## Revised Plans and Estimates for the Study

During January 1981, three sets of plans for the study were prepared in conjunction with Professor MacLennan, Dr. Byth and Ms. Rose. These plans (copies of which are attached) addressed the Investigation Programme at three levels:

- Overall Strategic Plan
- 1 Year Plan (1981)
- Plan for the Pilot Survey (to June 1981)

Since these plans were prepared, more detailed ones have been compiled in each of the main disciplinary areas of the study. We are currently monitoring progress against these plans on a weekly basis.

We look forward to the opportunity to give a presentation of the current plan and on progress.

COMMONWEALTH INSTITUTE OF HEALTH
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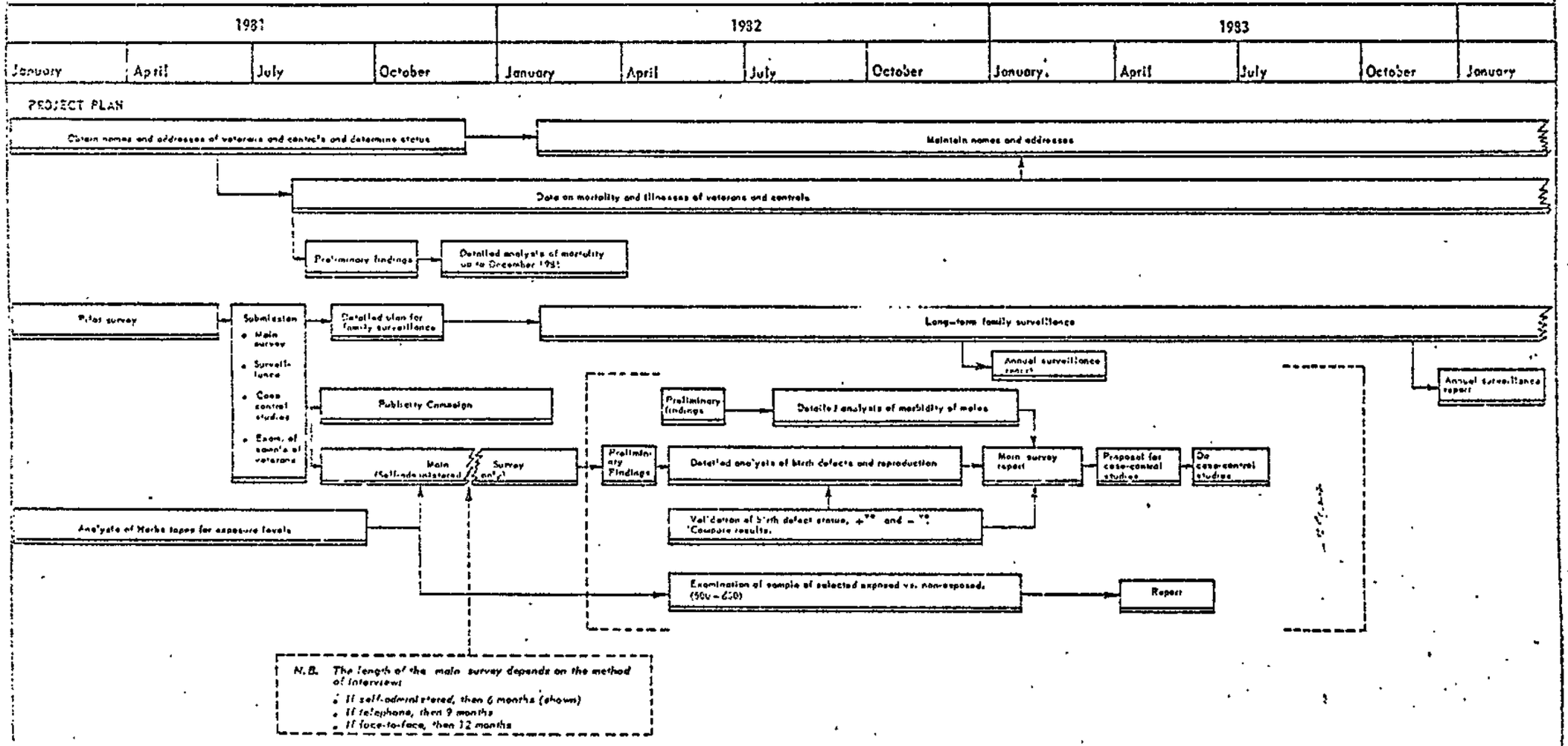
# PROJECT PLAN

RESEARCH PROGRAMME: "Agent Orange" Scientific Investigation
ASPECT OF INVESTIGATION: 3 Year Master Plan




MAJOR EVENTS

- Completion of Pilot Survey
- Analysis of Veteran Mortality
- Preliminary Findings for Main Survey
- Main Survey Report

| Version: 1.1 | Prepared by: Date..... | Approved by: Date..... | Comments: |
|---|---|---|---|

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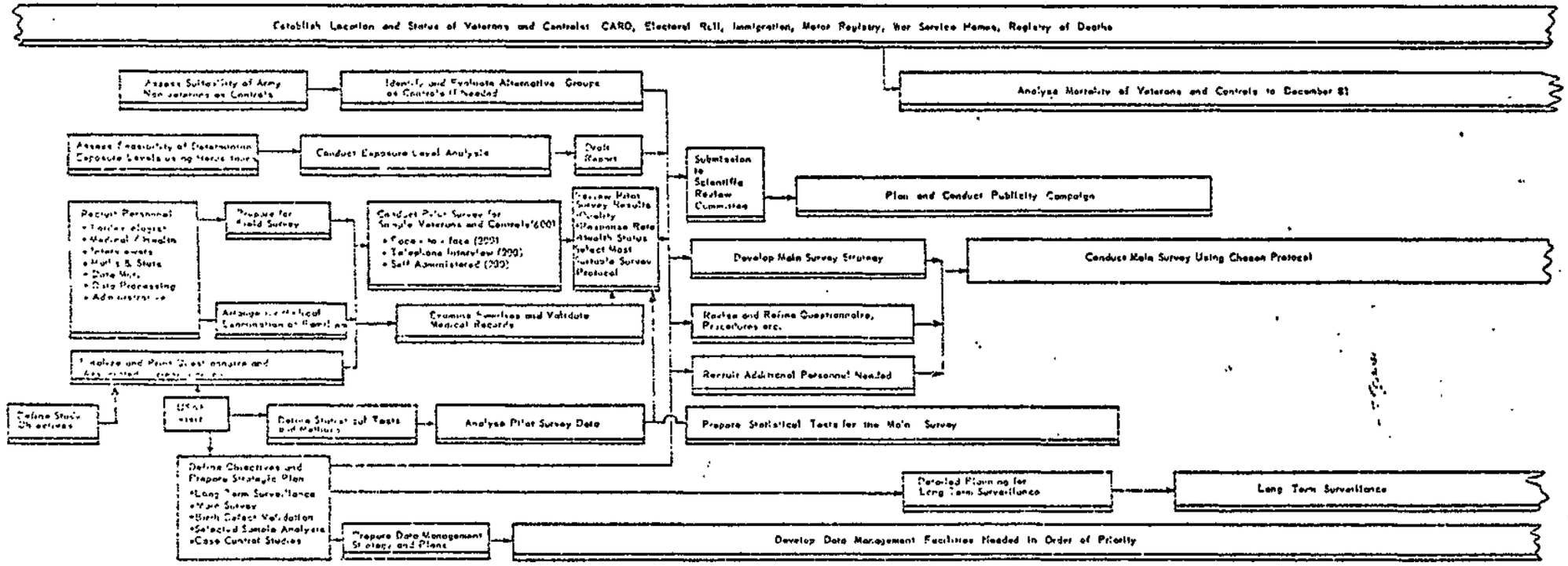
# PROJECT PLAN

RESEARCH PROGRAMME: "Agent Orange" Scientific Investigation
ASPECT OF INVESTIGATION: Master Plan for 1981

1981

| January | February | March | April | May | June | July | August | September | October | November | December |
|---|---|---|---|---|---|---|---|---|---|---|---|

PROJECT PLAN




MAJOR EVENTS

- Recruit Core Team & Pilot Survey Personnel
- Pilot Survey Started
- Pilot Survey Completed
- Recruit Main Survey Personnel
- Main Survey Started
- Long Term Surveillance Started

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COMMONWEALTH INSTITUTE OF HEALTH
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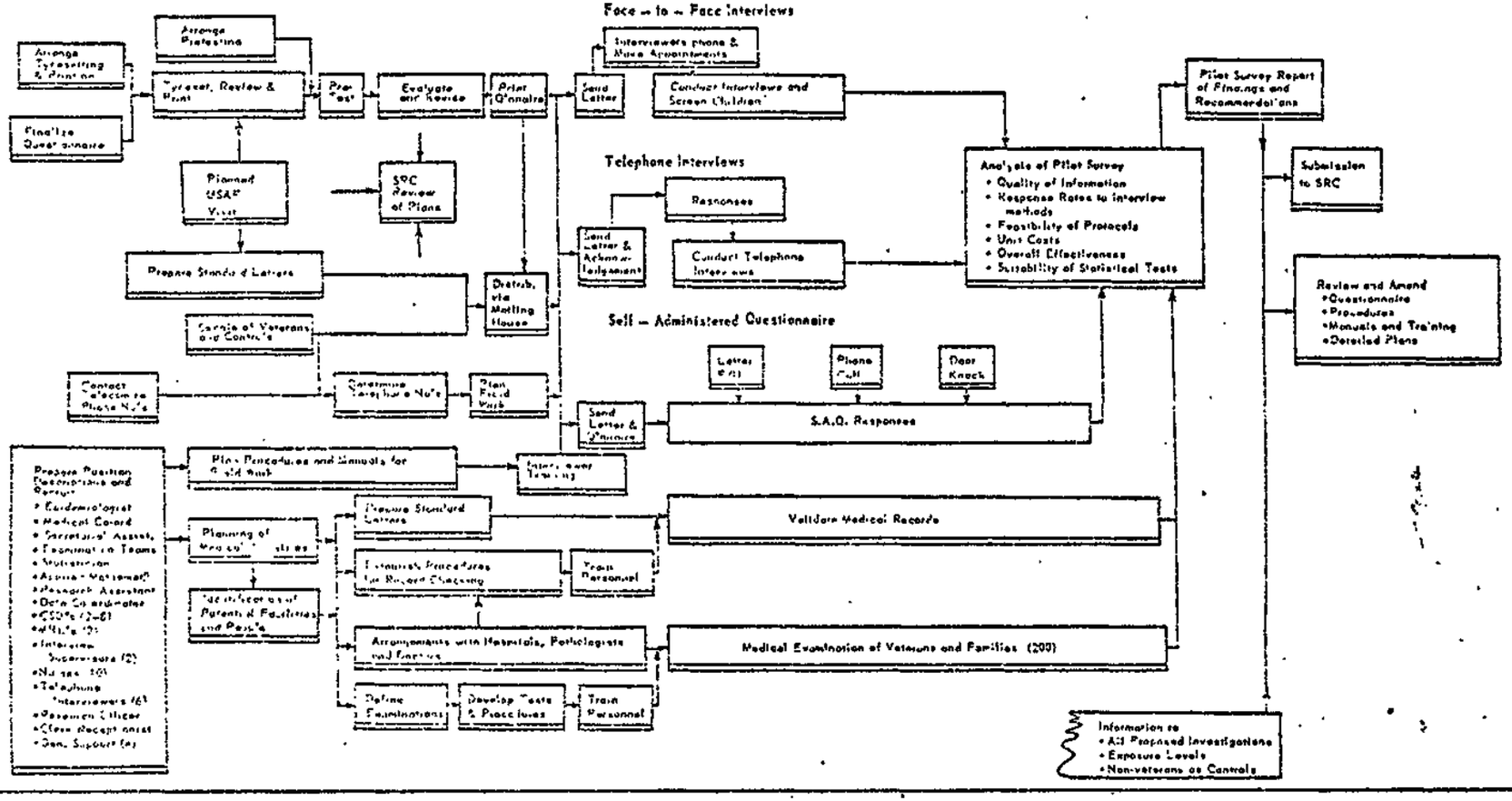
# PROJECT PLAN

RESEARCH PROGRAMME: "Agent Orange" Scientific Investigation
ASPECT OF INVESTIGATION: Pilot Survey

| January 31 | | | | | February | | | | March | | | | April | | | | May | | | | | June | | | | July | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 2 | 9 | 16 | 23 | 30 | 6 | 13 | 20 | 27 | 6 | 13 | 20 | 27 | 3 | 10 | 17 | 24 | 1 | 8 | 15 | 22 | 29 | 5 | 12 | 19 | 26 | 3 | 10 | 17 | 24 | 31 |

PROJECT PLAN




MAJOR EVENTS

- Recruit Key Personnel
- USAF Visit
- Commence Pilot Survey
- Complete Pilot Survey
- Submission to Scientific Review Committee

| Version 1.1 | Prepared by: Date | Approved by: Date | Comments: |
|---|---|---|---|