Inquiry into the Health Status of Children of Vietnam and Operation Grapple Veterans

June 1999

ADVISORY COMMITTEE ON THE HEALTH OF VETERANS' CHILDREN

8th June 1999

The Prime Minister

INQUIRY INTO THE HEALTH STATUS OF THE CHILDREN OF VIETNAM AND OPERATION GRAPPLE VETERANS

1. We have now completed our Inquiry into the Health Status of the Children of Vietnam and Operation Grapple Veterans in accordance with the Terms of Reference set by Cabinet on 27 July 1998. We are pleased, therefore, to present the enclosed Report of our findings.

Sir Paul Reeves, GCMG GCVO
Chairman

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Ministry of Health

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INQUIRY INTO THE HEALTH STATUS OF CHILDREN OF VIETNAM AND OPERATION GRAPPLE VETERANS

Chairman

Sir Paul Reeves, GCMG, GCVO, QSO, CF (Chair)

Members

Lt Gen A.L. Birks, CB, OBE, former Chief of Defence Force.

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INQUIRY INTO THE HEALTH STATUS OF CHILDREN OF VIETNAM AND OPERATION GRAPPLE VETERANS

1. EXECUTIVE SUMMARY

1.1 The principal focus of the Inquiry is the health status of the children of personnel who served in an official capacity in Vietnam during 1964 - 1972 and of those Naval personnel involved in supporting the British atmospheric tests at Christmas and Malden Islands during 1957 – 1958. Although the two scenarios have little in common, one chemical the other radiological, there have been long standing concerns among some veterans that they may have suffered exposures that could be responsible for the medical problems of their children.

1.2 In our preliminary research we realised that in the short time available, the relatively small number of people involved and the relative infrequency of the conditions under investigation, it would not be possible to undertake a reliable scientific study. A large amount of data relating to radiation has been derived from well documented, direct and measured exposure to nuclear weapons and other sources. The data for Agent Orange in Vietnam, however, has been taken from studies of indirect exposure and is complicated by herbicides and insecticides being present in the environment as well.

1.3. In order to ascertain whether any exposure to defoliants, herbicides and insecticides and nuclear radiation had been responsible for health problems in the children of veterans, we:

a. Undertook a survey of those military and civilian personnel who served in Vietnam and Operation Grapple I in order to identify their children who wished to provide us with details of their medical conditions;

b. Examined records of the exposure environment and safety provisions in place at the time to determine their adequacy and whether any exposure might have occurred;

c. Consulted scientific and medical experts;

d. Reviewed epidemiological evidence and assessments, and the conclusions of previous studies including those done in New Zealand and elsewhere; and

e. Discussed the concerns directly with veterans and their representatives, and examined the testimonials and documentation they provided;

1.4. In determining appropriate measures to assist those affected, we also took account of the status of Service men and women and the provisions of the War Pensions Act 1954.

1.5 Using these various approaches and different forms of analysis, our investigations do not convincingly demonstrate any causal connection between exposures to service personnel and health effects in their children. It is not possible to say with absolute certainty that those involved were never exposed to significant levels of radiation or chemical agents although the weight of evidence suggests this to be the case. In the case of radiation during Operation Grapple and chemical agents in Vietnam, we cannot give a categorical assurance that there is no linkage to the effects in the children. Furthermore, the information

available did not allow us to decide whether the incidence of health problems amongst veterans' children was any different to what occurs in the general population of New Zealand.

1.6 The Committee accepted the following categories of association adopted by the US Institute of Medicine:

a. "sufficient evidence of an association";

b. "limited/suggestive evidence of an association";

c. "inadequate/insufficient evidence of an association"; and

d. "limited/suggestive evidence of no association".

1.7 We believe that the first and second categories should be accepted by Government as sufficient grounds to qualify for medical treatment and social care similar to the non means tested provisions of the War Pensions Act 1954.

1.8 With the possible exception of spina bifida, categorised as "limited/suggestive evidence of an association", the current state of science and medical knowledge does not point to a link between exposure of Service personnel to nuclear radiation and to defoliants, herbicides and pesticides and the health of their children. All other conditions relating to the children of Vietnam veterans fell into the category of " inadequate/insufficient evidence of an association", while those pertaining to the children of Operation Grapple veterans were categorised as "limited/suggestive evidence of no association".

1.9. Nevertheless, the Committee is aware of the children's perception that they have been harmed by a parent's service either in Vietnam or in Operation Grapple. Despite strong evidence to the contrary, a scientific analysis cannot give a categorical assurance which will dispel that belief. Veterans and their families have a particular status in New Zealand and the Government has a duty to look after them, particularly given the liberal philosophy underpinning the War Pensions Act. We are recommending that the Government address the medical and social needs of the children by funding and providing a package of services through the Office of Veterans Affairs for case management, family counselling and genetic counselling where appropriate.

1.10 We recommend that:

a. Children of Vietnam and Operation Grapple veterans whose present or future condition, as a result of their parent's exposure to chemicals or radiation during service, falls into the epidemiological categories of "sufficient evidence of association" or "limited/suggestive evidence of an association", be provided with non means tested medical treatment and social care.

b. A programme of special assistance involving case management, family counselling and genetic counselling, be established for the children of Operation Grapple and Vietnam veterans.

c. The proposed Office of Veterans' Affairs be responsible for:

(i) The management of the special assistance programme;

(ii) The development and monitoring of the Register of Operation Grapple and Vietnam veterans' children;

(iii). The establishment of a research capability to provide

information on the health of veterans' children;

(iv). The provision of information and training for health professionals and others who work with the children of veterans;

(v). Adoption of a case management approach to veterans' children.

1.11. We recommend that funding to support these recommendations be provided by appropriation and administered by the Office of Veterans' Affairs.

2. INTRODUCTION

2.1 Following the 'Vietnam Remembered" commemoration in 1998, Cabinet directed that an inquiry be undertaken into the health status of children of New Zealanders who served in Vietnam and may have been exposed to chemical defoliants, or who participated in observations of nuclear testing in the Pacific in the late1950s and may have been exposed to nuclear radiation.

2.2 The principal focus of the inquiry was to be the children of veterans and any civilians who served in official capacities in either situation. Although the two situations had little in common, one being chemical and the other radiological, there had been long-standing concerns among some former servicemen who had served in one theatre or the other that they may have suffered exposures responsible for medical problems in their children.

3. TERMS OF REFERENCE

3.1 At its meeting on 27 July 1998, the Cabinet set the Terms of Reference for the Inquiry into the Health Status of Children of Vietnam and Operation Grapple veterans as follows:

> "Under the chair of Sir Paul Reeves, and comprising representatives of the Department of Social Welfare (War Pensions), the Department of the Prime Minister and Cabinet, the Ministry of Health, and the New Zealand Defence Forces, the Advisory Committee will undertake an Inquiry into the health status of children of New Zealanders who served in Vietnam in an official capacity, or who were involved in support for allied atmospheric nuclear testing in the Pacific.
>
> The purpose of the Inquiry is to ascertain whether any exposure to defoliants or nuclear radiation has been responsible for health problems in the children of those who served and, if so, to recommend appropriate measures to assist those affected.
>
> The inquiry will be based on a survey of all Service personnel and civilians who served in an official capacity who were deployed in Vietnam in the years 1964-1972, and all navy personnel involved in supporting the British

atmospheric tests and Christmas and Malden Islands in the period 1957 - 1958. On the basis of the survey data, and drawing on experience elsewhere and the findings of studies undertaken in other countries, the Advisory Committee should scope the extent, if any, of the problem and recommend appropriate options for Government to consider to assist with medical and social care.

In particular, the Advisory Committee should:

i. identify those exposed;

ii. determine the number of children possibly affected;

iii. analyse information and research on similar studies elsewhere and decide their relevance to the New Zealand situation;

iv. validate each case and define disability measures ; and

v. develop options for medical and social care for Government consideration.

3.2 The Cabinet determined that the composition of the Advisory Committee would be:

a. Sir Paul Reeves, GCMG, GCVO, QSO, CF, (Chair);

b. Margaret Faulkner QSM, War Pensions, Department of Social Welfare;

c. Patrick Helm, Department of the Prime Minister and Cabinet;

d. Dr Colin Feek, Ministry of Health; and

e. Lt Gen A.L. Birks, CB, OBE, Chief of Defence Force.

4. OUTLINE OF THE INQUIRY

4.1 In interpreting the Terms of Reference, we had to set limits on the scope of the exercise and make some assumptions so that our research was directed at the principal concerns.

4.2 At the outset it was clear that the nature of the inquiry and confidence in its outcome would be influenced by several factors:

a. The small number of people involved, especially in the case of Operation Grapple, and the relative infrequency of the conditions under investigation, meant that it would not be possible to undertake any reliable statistical analysis.

b. The passage of time (40 years since Operation Grapple, 30 years since Vietnam) would complicate the process of verifying personal circumstances;

c. The time available to the Committee to carry out the Inquiry, approximately nine months, precluded the possibility of commissioning new research or examining individual cases;

d. The issue under investigation was characterised by deeply entrenched personal convictions, complex medical and scientific questions, and sensitive concerns for those directly affected.

4.3 For these reasons, we came to the view that little would be gained by devoting resources to analyse the type and degree of individual exposure or work with particular cases. This requirement had been set down in the Terms of Reference at paragraph 3.1 (i) but it was beyond our ability to review individual cases in the time available.

4.4 Many cases had been examined over the years by general practitioners and medical specialists throughout New Zealand. However, few doctors have the experience or epidemiological knowledge of veterans' problems to determine whether there is a linkage between military service and the conditions diagnosed.

4.5 Because of the difficulty of establishing which, if any, New Zealand military personnel and civilians may have been exposed and the nature of that exposure, we made several critical assumptions at the start of our work:

a. All of the people who served in either theatre in an official capacity could have been exposed;

b. For both situations we would not attempt to assess what level of dose, if any, had been received and we would assume that any level of exposure might potentially lead to medical problems;

c. In the Vietnam situation, the Inquiry would encompass not just defoliants (Agent Orange) but herbicides and insecticides in case they separately, or synergistically, posed a genetic risk.

d. While we were made aware of the personal circumstances of a number of the children, time would not allow us to take account of the individual life histories or any confounding variables such as smoking or other environmental or hereditary factors.

4.6 The effect of these initial working hypotheses was to bias the analysis in favour of those claiming causal links, but we felt that these concessions were necessary in the early stages of our work to ensure that no valid evidence was excluded.

4.7 The requirement in the Terms of Reference to include civilians posed problems since their numbers were small and they had been engaged in a wide diversity of activities. Furthermore, no records had been kept of their personal details. We were able to contact a number of them, although the level of interest in the Inquiry was low.

4.8 It became clear that many of those who had served in either theatre had long been convinced that medical problems in their children were directly attributable to their military service.

4.9 Perception has been a major aspect of the Inquiry. While it was clear that the inquiry could not result in a definitive judgement, we were obliged to arrive at plausible, rational and defensible conclusions on which the Government could base future policy.

5. METHODOLOGY

5.1 It soon became clear that, with the small number of people involved and the relative rarity of the effects under consideration, no single line of investigation could be expected to provide sufficient evidence of an association between any exposure and the medical problems experienced by veterans' children. Consequently, we approached the Inquiry in several independent ways and, in sequence, we :

a. Undertook a survey of Vietnam soldiers and civilians, and Operation Grapple personnel in order to identify their children who wished to provide us with details of their medical conditions;

b. Examined records of the exposure environment and safety provisions in place at the time to determine their adequacy, and whether any exposure might have occurred;

c. Consulted scientific and medical experts;

d. Reviewed epidemiological evidence and the conclusions of previous studies including those from New Zealand and other countries; and

e. Discussed the concerns directly with veterans and their representatives, and examined statements and documentation which they provided.

5.2 While none of these complementary approaches could be expected to yield a definitive result, we were persuaded that if they showed a degree of concordance we could be reasonably confident in our conclusions.

5.3 In determining appropriate measures to assist those affected, we also took account of:

a. The status of Service men and women; and

b. The provisions of the War Pensions Act 1954.

6. IDENTIFICATION OF THOSE INVOLVED

6.1. In order to meet the requirement of the first and second Terms of Reference to identify those exposed and determine the number of children possibly affected, we used a basic questionnaire which is enclosed at Appendix One. We were able to determine that the veterans' group comprised:

a. 3,368 Service men and women who served in Vietnam;

b. 563 Naval personnel who served as part of Operation Grapple; and

c. 186 NZ civilians who worked in Vietnam during the war as teachers and aid workers..

6.2 Contacting some of the nominated veterans and civilians proved difficult. Many now live outside New Zealand; many families have changed their make-up and circumstance; and some veterans are simply unwilling to take part in a further survey. The Privacy Act also made it difficult to gain access to the details held by other organisations. Information about the release of the questionnaire was relayed to veterans through the various veteran organisations' newsletters. This was followed by a direct mail out of the questionnaires against an address list we had compiled from a variety of sources. This resulted in:

a. **Vietnam.** Of the 3,368 veterans on the list, addresses were found for 2,240; 1,354 veterans completed the questionnaire; 765 did not reply and 121 questionnaires were returned as a result of incorrect addresses.

b. **Operation Grapple.** Of the 563 Veterans on the list, addresses were found for 356; 164 veterans completed the questionnaire; 148 did not reply; and 44 questionnaires were returned as a result of incorrect addresses. Of the 207 for whom addresses were not found, 104 are now known to be deceased.

6.3. Although those who served in the two theatres can be identified, it was not possible to determine the degree of exposure, if any, to which individuals may have been subjected.

6.4 The veterans were generous with the information they provided in response to the questionnaire and the information provided gave the Committee a useful insight into the range of children's problems. The returned questionnaires were reviewed by Doctor Patrick Tuohy, Chief Advisor Child and Youth Health, Ministry of Health. His report at Appendix Two, conveys his concern that the very limited information made available through the questionnaires was insufficient to provide medical corroboration of the conditions suffered. The Committee was always mindful of that reservation but the questionnaire was useful for the purpose of identifying the children likely to have been effected and in ascertaining any major concerns.

6.5 Doctor Tuohy also noted that the sample of returned questionnaires was not representative of the major portion of the veterans' children. Therefore, Doctor Tuohy, was unable to determine whether the incidence of conditions that the children of veterans suffer is any different from that of the general population of New Zealand

7. THE VIETNAM ENVIRONMENT

7.1 The use of defoliants, pesticides, herbicides and other chemicals in Vietnam must be viewed in the context of the total operational environment. The use of chemical substances, while aiding prosecution of the war, attracted significant and growing international criticism because of the potential effect on humans. This section provides brief details on the main types of chemicals used in Vietnam.

7.2 Extensive aerial defoliation programmes were undertaken by US aircraft. There is only one recorded case of possible exposure of ANZAC troops to aerially delivered Agent Orange and that is the instance of the Australian C Company 5 RAR on 22 August 1969. It is known that New Zealand troops operated in areas that had been subject to previous defoliation but they were not in those areas at or near the time of defoliation.

7.3 Ground based defoliation programmes were also undertaken to control vegetation around the base area perimeters, weapon pits and on airstrips and landing points. "Local weed killing" around base areas was programmed during the wet seasons.

7.4 From 1962 until June 1971, herbicides were used for defoliation of natural vegetation and to destroy the enemy's in-country food supply. While troops may have been exposed to herbicides, there is only one recorded occasion when on 15 September 1967 troops from V Company, 2 RAR/NZ (ANZAC) might have been in or near an area being sprayed with an unidentified herbicidal type.

7.5 A wide range of insect borne diseases was endemic to Vietnam. They include various forms of malaria, bubonic plague, scrub typhus, dengue and encephalitis. Various measures were employed to combat these diseases, including spraying of insecticides by air and ground based means, trapping and baiting of insect hosts such as rodents, drainage and oiling of mosquito breeding grounds and the adoption of personal protective measures. Insecticides available included malathion, dieldrin, pyrethrins, DDT, diazinon and chlordene. Extensive aerial spraying programmes were undertaken at both Nui Dat and Vung Tau, and ground based spray systems, were used in Nui Dat.

Agent Orange

7.6. In the early years of the Vietnam War, the USA tried several aerial spray trials of herbicide mixtures to evaluate their effectiveness for defoliation and crop destruction. These went under the code names of Agents Purple, Blue, Pink, Green, Orange and White. Some were systemic defoliants, effective against woody and broad leaf plants, while others were non–systemic desiccants used against grasses, bamboo, rice and crops. Typically, they took one - two months to achieve maximum impact

7.7 Agent Orange, a 1:1 mixture of the two chlorophenoxy herbicides 2,4-D and 2,4,5-T eventually became the chemical defoliant most widely used in South Vietnam. Under an aerial spraying programme known as "Ranch Hand" approximately 9% of the total land area was sprayed between 1965 and 1970.

7.8 Debate on the effects of Agent Orange on people involved in the spraying operations began shortly after its introduction in 1965. The primary constituents of the herbicide are known to be of moderate toxicity. However, 2,4,5-T can contain a contaminant dioxin, generally known as TCDD, which is formed as an ineradicable impurity during manufacture and which is known as one of the most toxic man made chemicals. The toxicity varies slightly according to the form of the active ingredient but for 2,4-D in particular a dose of just 6 grams can prove fatal. Toxicity levels are not known precisely, but 2,4-D,the more toxic of the two, is thought to have an acute toxicity estimated at 50-100 mg/kg of body weight. The toxic dose for humans of 2,4,5-T is thought to be about 500mg/kg.

7.9 Both 2,4-D and 2,4,5-T can be absorbed from the gastrointestinal tract after ingestion or by inhalation. Little absorption occurs directly through the skin. Both are readily excreted and do not accumulate in the body.

Vietnam Exposure

7.10 The means by which soldiers might become contaminated with Agent Orange and other defoliants have been examined in many US and Australian reports. The Australian experience closely parallels that of the New Zealanders involved in Vietnam, and for the most part New Zealand soldiers operated with Australian forces (Australia had over ten times the number of soldiers New Zealand had in Vietnam).

7.11 The issue of exposure of Australian troops was fully investigated in several official Australian inquiries in the 1980s. Senate hearings throughout 1982, reported in the publication "Pesticides and the Health of Australian Vietnam Veterans" found no evidence of

direct exposure of Australians to Agent Orange or other phenoxy herbicides. They also rejected as "highly improbable " any association of birth defects with exposure to herbicides or insecticides.

7.12 The most comprehensive Australian investigation, the Royal Commission which sat from 1983 to 1985 examined all records of aerial spraying and checked them against the positions of Australian troops on the ground. They concluded that few if any Australians had been exposed to aerial spray, and that "five units of Australians were possibly within half-a-kilometre of spray path on only four days in the seven years of spraying." Detailed investigations of specific claims of direct exposure to Agent Orange could find no supporting evidence.

7.13 It was apparent that New Zealand soldiers who served in Vietnam came into contact with a variety of chemicals and while many were common to every day life, some were peculiar to the Vietnam environment. While evidence suggests that there is no link between Agent Orange and the problems in veterans, it is not known whether there might have been an aggregate effect from the exposure to all chemicals used in the Vietnam environment.

Environmental Protective Measures

7.14 New Zealand Service personnel were not involved in the direct handling of Agent Orange. There were very strict procedures in Vietnam for aerial spraying of Agent Orange from fixed wing aircraft to ensure that, as far as possible, it was not dropped directly onto personnel on the ground.

7.15 Aerial spraying of herbicides and insecticides was also subject to protective measures. Similarly, there were safety precautions within the Australian base areas pertaining to ground spraying of herbicides. Instructions were issued that equipment was to be cleaned; there was to be no smoking while handling or spraying; protective equipment, namely oil resistant gloves, aprons, goggles and masks were to be used; washing or bathing was required on completion of spraying or skin contamination; and utensils were to be sterilised in the event of illness or other medical symptoms. Nevertheless, there were reports of repeated incidents of non-compliance with these protective measures

8. RADIATION EXPOSURE OPERATION GRAPPLE

8.1 Following the New Zealand Government decision to support the Royal Navy during the Operation Grapple programme of atmospheric testing of British nuclear weapons, two RNZN ships, HMNZS Pukaki and HMNZS Rotoiti, were made available to act as weather ships during the tests in 1957 and 1958. The main task of the frigates was to collect meteorological information essential for the successful and safe conduct of the nuclear tests.

8.2 Operation Grapple consisted of two series of atmospheric tests: three detonations of thermonuclear devices over ocean in the vicinity of Malden Island during May and June 1957; and a further four detonations of thermonuclear devices plus two small nuclear fission ('atomic') devices in the area of Christmas Island (now part of Kiribati) between November 1957 and September 1958. All of the explosions were air bursts conducted at altitudes sufficient to ensure that no part of the fireball touched the surface.

*8.*3 In the course of the Operation Grapple tests, the New Zealand vessels were stationed at various distances between 20 and 150 nautical miles upwind from ground zero, the point on the ocean surface above which the devices were detonated. These distances

were chosen to ensure that the ships crews would be well outside the range of all radiative effects, and to fit with operational requirements for the provision of air/sea rescue if needed, anti-submarine surveillance, thermal flash monitoring, and water sampling. HMNZS Pukaki participated in all nine tests; HMNZS Rotoiti participated in the first four.

Environmental Protective Measures

8.4 While the New Zealand vessels were in the test area, they operated under the safety control of the Royal Navy. By this stage, the British had had a number of years of experience of nuclear testing and comprehensive safety provisions were in place. The RNZN vessels adopted similar safety protocols. Neither HMNZS Pukaki nor HMNZS Rotoiti had primary roles in the test monitoring, and were stationed upwind and well away from areas likely to be contaminated if a surface burst occurred accidentally. The explosions were arranged to take place high in the atmosphere to ensure that there would be no vaporisation or uptake of sea water that might create a contamination hazard or complicate the observations. Gamma rays and other initial radiation from the explosion were well attenuated within a few thousand metres.

8.5 On the ships themselves there were comprehensive safety procedures in place to minimise hazards in case of any unexpected occurrence. The ships could, if necessary, be sealed and they contained wash-down equipment. Radiation detection systems were in place which included both personal film badges, and integrating monitoring instrumentation and ratemeters by which doses at the time were estimated. These recorded no significant radiation. In his report at Appendix Three, Dr Andrew McEwan, Scientific Director, National Radiation Laboratory, noted that analysis conducted by the National Radiological Protection Board in the United Kingdom showed that of 21,358 participants in all British tests, only 1716 had non-zero radiation doses recorded, most of which were insignificant. There is no evidence, nor any suggestion from those responsible for radiological protection, that any RNZN vessel or crew member received any significant exposure to radiation during Operation Grapple.

9. CURRENT UNDERSTANDING

9.1 A large amount of data relating to radiation has been derived from well documented, direct and measured exposure to nuclear weapons and other sources. However, the data for Agent Orange in Vietnam has been taken from studies of indirect exposure, complicated by the fact that herbicides and insecticides were present in the environment as well. The Committee noted that the outcome of the major industrial accident at Seveso which involved the explosive release of dioxins, remains under scientific review.

9.2 In bringing together the information on these issues, we drew on the expertise of Professor Mark Elwood, Professor of Cancer Epidemiology, Department of Preventive and Social Medicine, University of Otago and Doctor Andrew McEwan, Director of the National Radiation Laboratory. Professor Elwood's report is enclosed at Appendix Four.

VIETNAM

9.3 In respect of exposure in Vietnam, Professor Elwood concludes that the most comprehensive scientific evidence of possible effects of Agent Orange and similar exposures on children is from the United States studies of Vietnam veterans. The 1996 and 1998 reports of the Committee to Review the Health Effects in Vietnam Veterans of Exposure to Herbicides (VAO 1996 and 1998), undertaken by the US Institute of Medicine, have been reviewed, as well as many other recent publications.

Categories of Association.

9.4. Professor Elwood adopts four categories of statistical association (not causation) as used in the VAO Reports in defining terms of associations. The four categories are weaker than the generally used epidemiological criteria for such assessments which seek to distinguish cause-and-effect relationships from mere association.

9.5. The 1998 VAO report expands on the interpretation of these four categories as follows:

a. **'Sufficient Evidence of an Association'**: That is, a positive association has been observed between herbicides and the outcome in studies in which chance, bias, and confounding could be ruled out with reasonable confidence. For example, if several small studies that are free from bias and confounding show an association that is consistent in magnitude and direction, there may be sufficient evidence for an association." There is sufficient evidence of an association between exposure to herbicides and the following health outcomes (in exposed veterans themselves, not in their children): soft-tissue sarcoma, non-Hodgkin's lymphoma, Hodgkin's disease, and chloracne.

b. **'Limited/Suggestive Evidence of an Association':** Evidence is suggestive of an association between herbicides and the outcome but is limited because chance, bias, and confounding could not be ruled out with confidence. For example, at least one high-quality study shows a positive association, but the results of other studies are inconsistent." There is limited/suggestive evidence of an association between exposure to herbicides and the following health outcomes (in exposed veterans themselves, not in their children): respiratory cancers (lung, larynx, trachea); prostate cancer; multiple myeloma; acute and sub-acute transient peripheral neuropathy; and porphyria cutanea tarda; and (as discussed below) spina bifida in the children of veterans.

c. **'Inadequate/Insufficient Evidence to Determine Whether an Association Exists'.** The available studies are of insufficient quality, consistency, or statistical power to permit a conclusion regarding the presence or absence of an association. For example, studies fail to control for confounding, have inadequate exposure assessment, or fail to address latency." The report lists 22 conditions under this heading, including spontaneous abortion, birth defects (other than spina bifida), neonatal/infant death and stillbirths, low birth weight, and childhood cancer in offspring.

d. **Limited/Suggestive Evidence of No Association.** Several adequate studies, covering the full range of levels of exposure that human beings are known to encounter, are mutually consistent in not showing a positive association between exposure to herbicides and the outcome at any level of exposure. A conclusion of "no association" is inevitably limited to the conditions, level of exposure, and length of observation covered by the available studies. In addition, the possibility of a very small elevation in risk at the levels of exposure studied can never be excluded." There is limited/suggestive evidence of *no* association between exposure to herbicides and the following health outcomes (in exposed veterans themselves, not in their children): gastrointestinal tumours (stomach cancer, pancreatic cancer, colon cancer, and rectal cancer); brain tumours.

9.6. Within the context of those categories, Professor Elwood's conclusions in respect of exposure in Vietnam are:

a. **There is no health outcome affecting the children or grandchildren of Vietnam veterans for which there is "sufficient evidence of an association".**

In the American Vietnam studies, the most detailed studies are those of "Ranch Hand" veterans, that is, Air Force personnel who were directly involved in handling Agent Orange and similar materials. Detailed studies of these veterans have been done, with extremely high participation, validation of questionnaire reports against medical records, and the use of a blood test which can assess current dioxin level and by back extrapolation allow an estimate of original dioxin exposure. These studies assess a very large number of health outcomes, and therefore some associations will arise purely by chance, and others may be real associations but may be due to factors other than Vietnam-type exposures. These studies assessed a wide range of effects on reproduction, birth defects, childhood cancer, and other outcomes. Other relevant studies include studies of civilians' exposures to dioxins and similar chemicals through accidental or occupational exposures, and case-control studies of reproductive outcomes in the United States, Canada, Europe, and Australia which assess Vietnam service or dioxin exposure along with other possible risk factors. In the 1996 and 1998 VAO reports, there was no health outcome affecting the children or grandchildren of veterans for which there was "sufficient evidence of an association" with relevant exposures. This conclusion is supported by the current review.

b. **For all other health outcomes, apart from spina bifida, there is "inadequate/insufficient evidence to determine whether an association exits".**

(i). The distinction between "inadequate/insufficient evidence to determine whether an association exits" and "limited/suggestive evidence of no association" is a judgement relating to the extent and detail of negative evidence, that is, evidence which does not suggest any association between Vietnam-type exposures and a health outcome. The distinction between these categories of conclusions requires a value judgement, which is likely to be variable between different reviewers, and requires a detailed and extensive review of all studies showing no association in their results. Although the main studies have been assessed, to review all the studies is outside the scope of the current review. The 1996 and 1998 VAO reports did not categorise any health outcomes in children in terms of the more stringent negative conclusion, that is "limited/suggestive evidence of no association". That is also the conclusion here.

(ii). This categorisation "inadequate/insufficient evidence to determine whether an association exits" can be interpreted in 'common sense' terms as follows. It means that the accumulated scientific evidence, considered with attention to the strengths and weaknesses of the studies available, does not suggest that any of these health outcomes are increased in children or grandchildren of Vietnam veterans: the most reasonable interpretation is that there is no increased risk. However, the studies are limited in size and scope, so it is not possible to 'prove' that there is no increased (or decreased) risk of these health events.

c. **For the occurrence of spina bifida in children born to veterans, the data show that the risk may be increased. This is considered as "limited/suggestive evidence of an association".**

For spina bifida, the 1996 and 1998 VAO Reports classify the results in terms of "limited/suggestive evidence of an association". The associations seen are based on small numbers of observations, but are seen in two partially independent studies of veterans, the Ranch Hand study, and the CDC Birth Defects study. Associations are also seen in some studies of civilians with occupational exposure to dioxins. An association was also seen in a questionnaire approach used in an earlier aspect of the U.S. veteran's study, but this was not confirmed by medical record validation. In contrast, no association with spina bifida was seen in the Australian veteran's study, in some civilian studies, or in the Seveso study, although all these studies are quite weak. None of these studies assessed the known other factors related to spina bifida, such as folic acid intake. The evidence is weak, and cannot be regarded as definitely establishing causality, but it is reasonable to accept the association as showing a possible causal association.

d. **The estimated frequency of spina bifida in births to exposed Vietnam veterans with substantial exposure to dioxin or similar chemicals is from 1 to about 4 per 1000 live births.**

This estimate is based on the American experience. Combining all categories of Vietnam service, for the spina bifida study, 454 fathers were identified who reported 1006 conceptions and 792 live births; there were 3 cases of spina bifida, a rate of 3.8 per 1000 live births (95% confidence interval 0 to 8.1 per 1000). These studies included aircrew with higher exposure levels than were likely for most New Zealand personnel. The frequency of spina bifida in the general population of New Zealand is fairly similar to that in the U.S. (around 1 per 1000 births), so these numbers allow some estimation of the expected number of similarly defined events in New Zealand veterans.

e. **A recent (1998) Australian questionnaire study of veterans, available as a draft report, has been reviewed but found not to be helpful.**

In its current form, this report (Commonwealth Department of Veterans' Affairs, 1998) has serious methodological problems, and the results are likely to be greatly affected by recall bias. Even in the American studies, which had much more rigorous methodology, results of questionnaire approaches were found to be unreliable unless validated by direct assessment of medical records. The assessment is included as Appendix 1 of this report.

f. **Valid conclusions on these issues can be confirmed only from studies with unbiased documentation of health outcomes in all births, and ideally in all known conceptions, to defined groups of veterans, with the use of appropriate comparison groups. Such studies require a high response rate, assessment of medical records or clinical examinations to verify health conditions, attention to methods to minimise bias in exposure recall, and attention to the likely effects of other risk factors.**

Questionnaires alone are insufficient. The difficulties with questionnaire studies seen in the U.S. and Australia have implications for the New Zealand questionnaire study currently being conducted, and make it clear that any interpretation of those results needs to be extremely cautious.

RADIATION

9.7 In his approach to the question of whether any radiation exposure to Operation Grapple veterans could lead to health effects in their children, Dr McEwan reasoned that there were two fundamental issues to be addressed:

a. what were the radiation doses received by the Service personnel ; and

b. what would be the effect on their offspring arising from any radiation received.

9.8 The New Zealand vessels were stationed well away from the testing zone and beyond range of prompt radiation. All nine detonations occurred, as planned, at altitudes sufficiently high to minimise the potential for subsequent fall out. The vessels and crews, operating under British safety procedures, were well prepared and had appropriate monitoring and safety equipment. In the event, no significant radiation was recorded, an outcome that was entirely consistent with other radiological monitoring throughout the test area.

9.9 A separate, if less directly informative, approach based on epidemiological analysis of New Zealand participants in Operation Grapple conducted by a group at Wellington Medical School came to essentially the same conclusion. A very small elevation in the rate of haematological cancers noted in that study could not be attributed to radiation received in 1957- 58 according to Dr McEwan. He noted also, that a much larger British study conducted by the UK National Radiological Protection Board found no increases in health effects in British participants at the Australian and Christmas Island tests.

9.10 Similar conclusions in respect of the Operation Grapple veterans have been reached by others. The annex to Dr McEwan's report comments on a recent paper presented to the New Zealand War Pensions Medical Research Trust Board by Dr Carol MacDonald. More generally, several atomic veterans studies involving American and British nuclear testing have concluded that "there was little or no evidence for a clear association between radiation exposure and increased mortality or cancer risk among veterans".

9.11 From these several lines of reasoning, Dr McEwan has concluded that on the first question concerning radiation doses to the Operation Grapple participants, "there is no evidence that the participants received any significant radiation exposures, and certainly no exposures that would give rise to any observable health effects."

9.12 On the second question concerning the more general issue of the hereditary effects of radiation exposure, Dr McEwan cites various authoritative reviews dealing with this issue. One pre-eminent authority, the United Nations Scientific Committee on the Effects of Atomic Radiation (UNSCEAR), has found that in respect of radiation "Epidemiology has not detected hereditary efforts in humans with a statistically significant degree of confidence". Large studies involving children born to survivors of the Hiroshima and Nagasaki bomb explosions, have failed to demonstrate hereditary effects.

9.13 The clear conclusion on this question, according to Dr McEwan, is that "no genetic effects have been demonstrated in irradiated human populations and that the risk coefficient for genetic effects in subsequent generations is small."

9.14 Overall, on the two fundamental issues relating to Operation Grapple hereditary effects, Dr McEwan has concluded that:

a. " there is no evidence of any radiation exposure of the servicemen in 1957-58 that could give rise to any health effects in the individuals themselves or their offspring;" and

b. "no radiation induced hereditary effects have been reported in human populations, even for those exposed to doses giving rise to deterministic effects."

10. OUR INTERVIEWS WITH THE VETERANS

10.1 As well as receiving direct correspondence, we undertook a series of meetings during February 1999 with veterans and their children at Auckland, Hamilton, Palmerston North, Wellington and Christchurch.

10.2 Both groups of veterans, those who had been involved in supporting the British atmospheric nuclear tests at Christmas and Malden Islands and those who served in Vietnam, are strongly convinced of the link between the medical conditions their children suffer and their own exposure to nuclear radiation and to herbicides, pesticides and insecticides. Some veterans have decided not to have children for fear of that risk. Other veterans have a deep seated concern that their military service and exposure to environmental hazards had led directly to the medical problems their children have experienced since birth.

10.3. Veterans' attitudes were consistent. They began with a very real anger that neither their service, nor its particularly hazardous nature, have received any acknowledgement from the Government which committed them to the operational environment in which they had been deployed. There was even greater resentment amongst veterans that no recognition had been given to the potential linkage between their service and their children' s medical conditions. Their greatest concern centred on what they saw as the injustice of their children's position. The veterans, in the main, accept that voluntary enlistment in our country's armed forces carries a risk they are prepared to accept - but as one veteran said "our children did not enlist". Consequently, they believe the State has a particular responsibility to safeguard the health of their children.

10.4. Accompanying the anger over their children's predicament were strong feelings of frustration and scepticism that anything would be done about it. Several groups spoke of the lack of follow-up on previous surveys. Nevertheless, the instigation by the Prime Minister of this present Inquiry has raised high expectations that at last their situation and that of their children will be recognised and more importantly, that something will be done about it.

11. THE VIEWS OF THE CHILDREN

11.1. Only a small number of veterans' children attended the discussions with the Inquiry Committee. Nevertheless, we found that the contributions they made were invaluable. We congratulate these young people for having the courage to speak about their conditions in the way that they did.

11.2. The most compelling impressions which the sons and daughters of veterans left with us were their anxiety about their condition and their genuine belief that it can be attributed to their father's military service. They were also concerned that they could pass on their condition to their own children. Some young couples have already decided not have children for fear of that consequence.

11.3 The young people who spoke to us were concerned about the impact of their condition on themselves and their inability to lead a normal life. Strongly allied to this was a desire for the origins of their condition to be recognised and for some special assistance to be given to them. We were impressed by the moderation and reasonableness of the measures they were seeking which centred not on monetary compensation but on ongoing access to treatment regimes

12. THE VETERANS' VIEWS

12.1. Veterans' concerns range from the philosophical to the pragmatic. As indicated, they stem from the perceived paucity of official acknowledgement of their service and the particular environment to which they were committed. This is compounded by anger and resentment at what veterans see as Government and systemic indifference, coupled with disregard and disbelief over their position and that of their children. Again, they cite the failure of any Government to take any action in response to previous surveys and submissions.

12.2 Every veterans' group spoke of the indifferent and incredulous stance taken by doctors when it was suggested to them that there might be a link between the environment in which they served and their children's medical condition. Veterans and their children constantly have to prove themselves in the face of sceptical and at times, hostile medical opinion. They find this demeaning and frustrating.

12.3. Veterans were concerned about the number of agencies they had to deal with to get assistance for their children. Moreover, there was a lack of coordination between the departments and agencies and a lack of consistency in their collective approach. All this added to veterans' frustration and their feeling of being mendicants on a system that really had an obligation to recognise their situation and treat them and their children with greater sympathy and understanding.

12.4. Many veterans and their families have made considerable personal sacrifice in raising children with disabilities and poor health. These people have spent a considerable proportion of their income to gain access to medical treatment and much of this expenditure has been incurred on a continuing basis.

12.5. Veterans had some specific concerns. They spoke of the lack of any facility for children to get special assistance and they were greatly concerned for the welfare of their children once the parents had died.

12.6. Veterans were also concerned about the assistance available to the parents and caregivers involved in looking after children with medical conditions and disabilities. Many of these people, most of them veterans and their spouses, had been shouldering a considerable and stressful burden for a prolonged period without any recognition or assistance.

13. THEIR PROPOSALS FOR REMEDIAL MEASURES

13.1. We were impressed by the moderate and pragmatic measures proposed by veterans to ameliorate their children's situation. There was an occasional call for compensation, which the Committee made clear to the proponents was not part of the

Terms of Reference, but in the main, suggestions for additional assistance were logical and reasonable.

13.2. Every group sought recognition of their service from the Government which had "put them in harm's way". They also sought an acknowledgement of a potential linkage between their exposure to nuclear radiation or to herbicides, pesticides and insecticides and the medical conditions of their children.

13.3. It was also suggested that medical practitioners be selected to serve individually or on panels to examine the veterans' children. These doctors would receive special education and training in the potential effects of exposure to nuclear radiation and to herbicides, pesticides and insecticides

13.4. There was support for a single agency to provide support and assistance for veterans and their children in the form of a Department or Office of Veterans' Affairs. Veterans generally favoured the suggestion that this agency be positioned within the New Zealand Defence Force organisation, providing it retained a degree of autonomy. There was agreement that one of the functions of this agency would be to implement any proposals for better assistance to veterans' children.

13.5. There was also support for a planned programme of genetic counselling to be made available to veterans and their children. Many veterans also called for better and more consistent communication with themselves and their children and they felt that this would be achieved if a single agency was responsible for their welfare.

13.6. There was unanimous agreement that general counselling should be made available to parents, families and caregivers responsible for looking after veterans' children with medical conditions and disabilities. Many of these people have been under considerable stress for prolonged periods and they have carried the burden of concern that their military service may have contributed to their children's condition.

13.7. Other proposals for the provision of assistance to veterans' children included:

a. Special help for chronically unemployed and under-employed children;

b. Reimbursement of special training expenses;

c. Dispensation for life and medical insurance; and

d. Reimbursement of travel costs associated with gaining access to special medical treatment.

13.8. One group proposed that a trust be established to safeguard the welfare of veterans' children in perpetuity. The Committee's view on this suggestion, and on the other recommendations made by veterans is outlined later.

14. THE SPECIAL STATUS OF VETERANS

14.1. Servicemen and women occupy a unique position within our society. A number of characteristics confer this special status on them. They swear allegiance to the Crown and take a solemn oath to serve their country. In so doing they submit themselves to a code of military discipline and law which is additional to the laws of the country which apply to all citizens. In effect, they are subject to a second judicial system arising from their status

and this results in normal human failings and misdemeanours becoming serious offences which attract a wide range of penalties.

14.2. Service personnel accept this situation and serve their country voluntarily.

14.3. At the same time, service men and women, in the interest of the State and its citizens, forego the right of freedom of action and choice enjoyed by all other citizens. In particular they accept real limitations on their rights of redress from the Crown especially in times of war and during military operations.

14.4. Additionally, they place their lives and their welfare at the disposal of the Crown. They acknowledge that the Crown can deploy and employ them wherever it wishes to do so. Even more significantly, they accept that the Crown (the Government) can commit them, compulsorily, to situations where their lives are at risk and that ultimately their service to their country may result in the loss of their life. They also accept that their lives and their health may be at risk from the environments in which they are deployed and that they may be exposed to additional hazards beyond those usually associated with traditional military operations, such as disease and other conditions which could have a deleterious impact on their health and well-being.

14.5. The special nature of service in our nation's armed forces has a profound effect on the families of military personnel. Spouses and partners can be subject to enforced and stressful separations from their families, often at short notice..

15. THE GOVERNMENT'S RECIPROCAL OBLIGATIONS

15.1. Against this background, Servicemen and women pursue their profession on the basis that the Crown will attend to their well being and to the welfare of their families. In effect, by virtue of their oath of allegiance, members of the Armed Forces enter into a unilateral undertaking to serve the Crown and State. Inherent in this understanding, is an unspoken contract that the Crown will look after them and their families. Indeed, confidence that this will be the case is fundamental to the morale of Service people and crucial to their motivation to join and to remain in the armed forces and if need be, to sacrifice their own life on behalf of the Government and fellow citizens.

15.2. The nature of military service, places a special reciprocal obligation on Governments, as agents of the Crown, to safeguard the well being of the Service personnel who act in the Government's interests and the citizens they represent. Families play an important part in maintaining our military capability and we believe that Government also has a responsibility to support their welfare as well.

15.3. The Government's responsibility is embodied in the War Pensions Act 1954. It is through this Act that the Government reciprocates the trust Service people place in the Crown when they accept the extraordinary conditions of their employment. The War Pensions Act places obligations on the Government to safeguard the welfare of those who act compulsorily in furthering its national security interests.

15.4. There is no guidance in the War Pensions Act 1954 on the criteria to be used when declaring an operational military situation to be covered by the Act's provisions. In addition, there are very few people outside the military who have had experience of military service. There is, therefore, the potential for the special nature and the associated risks of service in our country's defence force not to be recognised. This situation arises from the general lack of understanding across New Zealand society as a whole of the special status, of members of our nation's armed forces.

16. THE WAR PENSIONS ACT 1954

16.1 The New Zealand Government's method of compensating Service personnel for injuries, disabilities or disease processes as a result of military service traditionally has been through the provisions of the War Pensions Act 1954. Pensions for death or disablement as a result of military service in a war have been available in this country since the introduction of the Military Pensions Act of 1886. While the original Act has undergone many alterations over the years, the basic principles of pensions, related allowances and treatments for war related disabilities have remained in the current War Pensions Act 1954 and War Pensions Regulations 1956.

16.2. The fundamental philosophy on which New Zealand's war pension legislation is based is that of giving veterans who have served in a war or emergency, the benefit of the doubt in terms of demonstrating the attributability of a medical condition to their military service. The establishment of absolute certainty or even limited suggestion that a condition is attributable is not required. The balance of probability is not used in war pensions decision making. Pensions are payable where a medical assessment of a condition states that it can not be disproved that the condition could have had its genesis in the Service environment. This characteristic of New Zealand's War Pensions Act makes it fundamentally different from other countries' war pensions legislation which, in general, require legal proof before accepting attributability. The New Zealand philosophy is indicative of our Government's acceptance of its obligation to safeguard the welfare of Service men and women.

16.3 The Act provides:

a. War Disablement pensions that are compensatory in nature and based on service related injury, disability or disease. The pension rate is fixed at the current level of disability with the pension payments being tax free. Pensions are paid in 5% steps with the 5% pension rate currently set at $7.31 and the 10% rate at $146.15. Pensions are increased annually based on the CPI adjustment.

b. Treatment for accepted service related conditions.

c. A number of additional allowances for specific disabilities i.e. clothing allowance.

d. Surviving spouses' pensions in certain circumstances.

e. Children's bursaries in specified cases.

16.4 An important feature of these provisions is that none of the benefits available under the Act are means tested.

16.5 In April 1967 the Government accepted service in Vietnam as service in connection with an emergency under the provision of Section 80A of the War Pensions Act. This decision allowed Vietnam Veterans to be provided with the same pensions, allowances and treatment as provided to World War I and II Veterans.

16.6 The Government extended the provisions of Section 80A to Operation Grapple Servicemen on 31 March 1998.

16.7 War disablement pensions are awarded for any injury, disability or disease process that could have originated during service. Section 17 of the Act is used to decide war disablement pension eligibility. This Section contains a reverse onus of proof and presumptions which allow the benefit of the doubt to be awarded to the applicant. The balance of reasonable probability is not used in war pensions decision making.

17. WEIGHING THE SCIENTIFIC DATA

17.1 In interpreting the information presented during the Inquiry, and in arriving at conclusions about its overall implications, we drew on methods used in epidemiological research. The Operation Grapple and Vietnam situations were not of a type in which normal scientific criteria could be applied, but we were conscious of the need to work within a framework that was consistent and recognised in the medical and scientific communities. Epidemiologists have developed observational, that is non-experimental, methods for interpreting data gathered under uncontrolled conditions that we concluded were appropriate for both situations under review.

17.2 As is the case with all observational data, particular care has to be taken in the interpretation of epidemiological outcomes. It may be true that an epidemiological association seen in certain situations could directly reflect an underlying cause-and-effect relationship, but there may be other explanations. Random chance, bias or systemic effects may well create artificial associations, especially where the effects are small. Moreover, in uncontrolled conditions there are many ways in which confounding factors may influence the outcome in indirect ways. For instance, factors which may seem to be more important may not themselves be the cause of the problem but may be indirectly related to some other genuine causal factor.

17.3 It was not possible for this Inquiry to differentiate between exposures that may have been received during Operation Grapple or Vietnam service and normal life-time exposure in New Zealand. All New Zealanders live in an environment in which they are regularly exposed to a wide range of radiation, both natural and artificial, and to chemical agents such as insecticides, and herbicides. Background levels vary from place to place, and individuals, throughout their lives, experience different levels of exposure through various exposure routes such as soil, air, food etc. The issue about service in Vietnam and Operation Grapple, however, relates to the level of exposure to those agents and, in Vietnam, to the potential synergy between them.

17.4 The interpretation of epidemiological analysis is a complex business. We adopted a framework involving four levels of "association" that have become the standard for the US Institute of Medicine in its biennial series of reviews entitled "Veterans and Agent Orange Update"

17.5 These categories refer to levels of association which do not necessarily imply causation. In epidemiological practice there are more stringent criteria of causality involving measures of consistency, coherence, specificity, and strength of association. These are applied to decide whether there might be explanations other than the presumed cause-and-effect relationship.

17.6 The consequences of using this approach in our Inquiry is a bias in favour of accepting a condition as potentially related to hazardous exposures. We were willing to take this approach because it was consistent with our inclination throughout the Inquiry to regard all claims sympathetically.

18. CONCLUSIONS

18.1 In reaching conclusions on such a complex and difficult subject which is surrounded by understandable emotion, we took into account a broad mix of factors, including the exposure environment and safety provisions, our survey of veterans, the outcomes of epidemiological studies, the status of Service men and women and their families, the nature of our national war pensions legislation and its provisions, and the views of the veterans and their children. We took note of relevant overseas scientific findings and medical research and in arriving at our recommendations, we adopted a sympathetic approach, consistent with the New Zealand legislative environment.

18.2. Except perhaps in one case, our review of epidemiological studies and the current state of scientific and medical knowledge does not point to a link between the exposure of military personnel to nuclear radiation and to defoliants, herbicides and pesticides and the health condition of their children. Many veterans are convinced of such a linkage but our review of the scientific and medical literature does not support that conviction.

18.3 While all available evidence may suggest otherwise, it is not possible to conclude categorically that there is no such linkage. As a general rule, it is very difficult in science to prove a negative effect; a lack of evidence is not necessarily a lack of evidence of an effect. While any undetected genetic effect attributable to exposure to nuclear radiation or to defoliants, herbicides and pesticides is likely to be small, the possibility of such an effect cannot be entirely discounted.

18.4 Scientific and medical research in this area still continues. This is exemplified in the programme being undertaken in the United States under the auspices of the Committee to Review the Health Effects in Vietnam Veterans of Exposure to Herbicides sponsored by the American Veterans' Affairs Office. The US Committee updates and revises it findings biennially. We believe that it is essential that the new Office of Veterans Affairs in New Zealand should accommodate the results from both current research and any future research that has been subject to rigorous evaluation and peer review.

18.5 No condition examined as part of the Vietnam epidemiological studies review fell into the category of " sufficient evidence of an association". One, spina bifida, was placed in the category "limited/suggestive evidence of an association". We accept that a value judgement was required in reaching that conclusion, given the degree of uncertainty of the information available. No conditions were categorised as " limited/suggestive evidence of no association". All other conditions were classified as under the less stringent category of "inadequate/insufficient evidence to determine whether an association exists"'. While this categorisation may appear generous, we accept that it reflects the current state of science and medical research in this area.

18.6. There is no evidence that any hereditary effects in the children of Operation Grapple personnel may be attributed to exposure to radiation arising from their parent's service. All conditions in respect of radiation exposure, therefore, were assigned under the category of "limited/suggestive evidence of no association".

18.7. When we considered the Terms of Reference which required us to recommend options for the medical and social care of veterans' children, we were conscious that many veterans and their children have long harboured a perception that they have been harmed by military service. Scientific analysis can not give a categorical assurance to dispel that belief.

18.8. In arriving at our recommendations, we took account as well of the special status of our Service men and women and their families. We noted the Government's obligation to safeguard their welfare and the philosophy behind our national war pensions legislation which gives practical expression to that obligation.

18.9. Against this background, we concluded that the children of Operation Grapple and Vietnam veterans should be given a package of special assistance to deal with the social and medical circumstances they face.

18.10. We endorse the Government's decision to establish an Office of Veterans' Affairs which should be the agency responsible for the provision of special assistance to the children of veterans. If special care is to be delivered effectively, this responsibility should include the compilation of a Register of the children and their medical conditions. However, because of the Privacy laws, the decision to enter a name on the Register must lie with the individual veterans and the children

18.11. We also recommend that the Office of Veterans' Affairs be responsible for establishing a capability to provide ongoing research into the health of veterans and their children and the effects of environmental hazards such as exposure to nuclear radiation and defoliants, herbicides and pesticides. Science in this area continues to evolve and New Zealand should have ongoing access to the latest scientific and medical knowledge. We see the publication and promulgation of relevant material in medical and scientific journals as important in promoting a wider professional awareness.

18.12. An important part of the special medical assistance needed by the children of veterans is the identification and selection of specialist medical practitioners throughout the country who, individually or on panels, would advise on the health status of veterans' children and assist in determining the assistance they should receive. We envisage the Office of Veterans' Affairs being responsible for identifying such a group of doctors and for arranging for these medical personnel to be given special professional training and educational opportunities, to advance their knowledge and expertise within the field.

18.13. Case Management for each veteran's child should be adopted as the basis for the delivery of special assistance to them by the Office of Veterans' Affairs. That assistance should include the availability to veterans and their families of specialist counselling, including genetic counselling, if required.

18.14. Our final conclusion is that children of Vietnam veterans who suffer from spina bifida, a condition that falls into the category of "limited/suggestive evidence of an association" should be provided with non means tested medical treatment and social care. We also believe that if ongoing research shows that a medical condition currently grouped in the category "inadequate/insufficient evidence to determine whether an association exists" is reclassified in the future so as to fall into one of the two other and higher epidemiological categories, then the non means tested medical treatment and social care should also be applied to those reclassified conditions.

19. RECOMMENDATIONS

19.1 We recommend that:

a. Children of Vietnam and Operation Grapple veterans whose present or future condition, as a result of their parent's exposure to chemicals or radiation during service, falls into the epidemiological categories of "sufficient

evidence of association" or "limited/suggestive evidence of an association", be provided with non means tested medical treatment and social care.

b. A programme of special assistance involving case management, family counselling and genetic counselling, be established for the children of Operation Grapple and Vietnam veterans.

c. The proposed Office of Veterans' Affairs be responsible for:

(i). The management of the special assistance programme;

(ii). The development and monitoring of the Register of Operation Grapple and Vietnam veterans' children

(iii). The establishment of a research capability to provide information on the health of veterans' children;

(iv). The provision of information and training for health professionals and others who work with the children of veterans.

(v). Adoption of a case management approach to veterans' children.

19.22. We recommend that funding to support these recommendations be provided by appropriation and administered by the Office of Veterans' Affairs.

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Appendices:

1. Questionnaire

2. Report by Dr Patrick Tuohy, Chief Advisor Child and Youth Health, Ministry of Health

3. Report by Dr Andrew McEwan, Scientific Director, National Radiation Laboratory

4. Report by Professor Mark Elwood, Professor of Cancer Epidemiology, Department of Preventive and Social Medicine, University of Otago

Appendix 1

QUESTIONNAIRE FOR THE ADVISORY COMMITTEE ON THE HEALTH OF VETERANS' CHILDREN

Service Details

1. Surname ..... First Names.....

2. Address.....

3. Phone number.....

4. What was/is your regimental number.....

5. When did you serve in Vietnam: From .....(Month) .....(Year)

   Until: .....(Month) .....(Year)

6. What organization, unit or sub-unit did you serve with? .....

7. Where in SVN did you serve?.....
   (List provinces/cities)

8. What was your appointment/ trade during your tour in SVN?.....

9. Are you currently in receipt of a War Disablity pension, if so for what disabilities? .....
   .....

.....

Details of Children

10. Do you have any natural children ?.....

11. How old are your children? M/F .....years M/F.....years
    M/F.....years M/F.....years
    M/F.....years M/F.....years

12. Do all of your children enjoy good health? Yes/No

13. If you answered "No", please give general details (attach separate sheet if you wish) and attach GP note outlining disability.....
    .....
    .....

14. Do you have any grandchildren from your natural children? Yes/No
    How many?.....

15. Do your grandchildren enjoy good health? Yes/No

16. If you answered "No", please give general details and attach GP note outlining disability
    .....
    .....

.....

Personal Declaration: I give my consent for the information provided in this form to be used for the purpose of assisting the inquiry into the health of veterans' children.

I wish / do not wish to be contacted again in respect of further study into my personal circumstances.

Signed..... Dated.....

QUESTIONNAIRE FOR THE ADVISORY COMMITTEE ON

THE HEALTH OF VETERANS' CHILDREN

Service Details

1. Surname ..... First Names.....

2. Address.....

3. Phone number.....

4. What was/is your regimental number.....

5. When did you serve in OP GRAPPLE From .....(Month) .....(Year)

   Until: .....(Month) .....(Year)

6. What organization, unit or ship did you serve with? .....

7. What was your appointment/ trade during OP GRAPPLE?.....

8. Are you currently in receipt of a War Disablity pension, if so for what disabilities? .....
   .....

.....

Details of Children

9. Do you have any natural children ?.....

10. How old are your children? M/F .....years M/F.....years
    M/F.....years M/F.....years
    M/F.....years M/F.....years

11. Do all of your children enjoy good health? Yes/No

12. If you answered "No", please give general details (attach separate sheet if you wish) and attach GP note outlining disability .....
    .....
    .....

13. Do you have any grandchildren from your natural children? Yes/No
    How many?.....

14. Do your grandchildren enjoy good health? Yes/No

15. If you answered "No", please give general details and attach GP note outlining disability
    .....
    .....

.....

Personal Declaration:

I give my consent for the information provided in this form to be used for the purpose of assisting the inquiry into the health of veterans' children.

I wish / do not wish to be contacted again in respect of further study into my personal circumstances.

Signed..... Dated.....

Appendix 2

MINISTRY OF HEALTH
MANATU HAUORA

133 Molesworth St
P.O. Box 5013
Wellington
New Zealand
Phone (04) 496 2000
Fax (04) 496 2340

Ref. No _____

REPORT

VIETNAM VETERANS' CHILDREN AND GRAPPLE

Dr Patrick G Tuohy
Chief Advisor Child and Youth Health
Ministry of Health

Summary
This report is based on the very limited information provided to me regarding the claimed health problems suffered by a sample of veteran's children from these two theatres. No information was available to provide independent medical corroboration of the conditions suffered. It was clear that this sample was not even a major proportion of all the children of these veterans. Nevertheless some rates of illness were significantly higher than national averages, and suggest that further study should be undertaken to determine whether the prevalence of these illnesses is in fact truly increased in veteran's children and whether a cause an effect relationship exists.
My review has been unable to provide any information which indicates that any individual has suffered an illness or disability as a direct result of a parent's or grandparent's exposure to the environment toxins or radiation respectively.

Methods
I reviewed all of the available case notes for the children, and have coded the provided list of children (Vietnam only) with number codes according to the following key:

1. Conditions definitely due to prenatal or parental exposure to toxins.

2. A condition which has probably arisen prenatally.

3. Insufficient information.

4/5. A condition which probably occurred postnatally in any child on the basis of genetic predisposition and/or exposure to such as infection, an exogenous agents or allergens.

It must be noted that the rates of the conditions in the veteran's children are calculated using the case list provided as a denominator. These rates are indicative only and are not directly comparable with population rates, as the true denominator (ie all children of servicemen who served in Vietnam on in Operation Grapple) is unknown

Findings
The coding does not attempt to classify children on the basis of likelihood that the illness was due to exposure to toxic chemicals. Overall around 30% of the conditions are likely to have arisen prenatally, 50% postnatally and the remainder could not be adequately classified. Of the prenatally originating conditions most are of unknown cause.

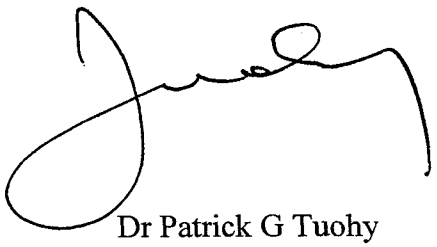
All of the abnormalities or illnesses described are present, as far as I can interpret them from the description in the files, in the population at large. However, the proportions of problems identified in this sample are, in some cases, higher than those present in the whole population, or in less selective samples. This higher rate could be due to over-reporting, misdiagnosis, random fluctuations present in small samples, sampling errors, or it may indeed be due to the true over-representation of cases among the children of veterans. The only well defined conditions which show substantial differences between

the rates in the sample and the general population are spina bifida, congenital eye problems and Down syndrome. The clinical and statistical relevance of these differences can only be determined by reference to other studies conducted using appropriate scientific methodology.

The crude rates of specific conditions and reference values from NZ populations of the same era (1960's and 70's) are shown in Table 1 (Vietnam) and Table 2 (Grapple). Not all conditions are markedly different from reference values.

Discussion

I have not applied statistical tests to determine the significance of the differences between the rates since the sample of veterans children described in this report cannot be described as a random sample from a known population. The information in fact is collected from a very non-random sample, which is the families of servicemen, not the entire New Zealand population. This means we are not comparing two identical populations. Secondly the sample evaluated consists of a sub-set of those children of veterans, about whom the parents have a health concern. This will clearly bias the sample towards those with a problem to report, as those with no perceived problem may decline to return the questionnaire. The total number of children of veterans (denominator) is unknown, but is likely to be substantially greater than the number represented in this survey. For that reason the given rates in the sample will significantly overestimate the true rate in the children of the veterans.



Dr Patrick G Tuohy
Chief Advisor
Child & Youth Health

Table 1 - Vietnam

Congenital Defect	No	Rate in Sample	Approx rates 1960s - 1970s	Notes
Club Feet (talipes)	9	12.1/1000	5.2/1000	Known to be more common in Maori children.
Heart Defects	9	12.1/1000	5.2/1000	
Spina Bifida	7	9.4/1000	1.6/1000	
Cleft Lip/Palate	7	9.4/1000	1.9/1000	
Hypospadias	3	4.0/1000	3.0/1000	
Down Syndrome	6	8.0/1000	1.3/1000	
Choromosones (other)	2	2.7/1000	1.2./1000	1990 Dept of Health data
Genital	4	5.2/1000	11.63/1000	1993 Plunket data
CNS	4	5.3/1000	0.88/1000	Not well described
Congenital Respiratory	2	2.7/1000	0.46/1000	1993 Plunket data
Renal	9	12.0/1000	1.63/1000	
Musculo Skeletal	28	37.5/1000	13.0/1000	1993 Plunket data
Eye (Congenital)	3	4.0/1000	0.7/1000	1993 Plunket data
Ear	4	5.3/1000	4.0/1000	1993 Plunket data

Table 2 - Grapple

Congenital Condition	No	Rate in sample	Ref. Rate/1000
Ears/ENT	2	8.0/1000	4.0/1000
Eyes	4	16.0/1000	0.7/1000
Orthopaedic excl. talipes	2	8.0/1000	5.2/1000
Hypospadias	1	4.0/1000	3.0/1000
Cardiac	5	20.0/1000	5.0/1000
Renal/Bladder	3	12.0/1000	1.63/1000
Down Syndrome	2	8.0/1000	1.3/1000
Spina Bifida	2	8.0/1000	1.6/1000
Cleft Lip/Palate	1	4.0/1000	1.9/1000
Chromosome (other)	2	8.0/1000	1.2/1000

Appendix 3

REPORT TO THE ADVISORY COMMITTEE
ON THE HEALTH OF VETERANS' CHILDREN

REPORT ON THE POTENTIAL FOR RADIATION INDUCED GENETIC EFFECTS IN CHILDREN OF CHRISTMAS ISLAND VETERANS

A C McEwan

May 1999

Preface

In October 1998 I was asked to provide Professor Mark Elwood of the University of Otago with comments on the likelihood of any radiation-induced genetic effects in the offspring of veterans who had served with the New Zealand Navy during the time of its participation in the British nuclear test series in 1957-58, based at Christmas Island. Professor Elwood was undertaking a review for the Advisory Committee of evidence on the effects on the health of veterans' children arising from potential or actual exposure of Vietnam war veterans to defoliants. Subsequently in December 1998 I was asked to provide comment on publications which had been forwarded for the Advisory Committee's attention which raised concerns about possible effects on Christmas Island veterans of radiation exposure. This report is a summary of advice provided in response to these two requests. The first issue is addressed in the body of the report. The comments on publications are included as an appendix.

THE POTENTIAL FOR RADIATION-INDUCED GENETIC EFFECTS IN THE OFFSPRING OF CHRISTMAS ISLAND VETERANS.

There are two fundamental issues to be addressed in the study of the health of children of veterans who were present for some of the tests in the Christmas Is region in 1957-58. One is, what were the radiation doses received by the men, and the second is, what would be the effect on their offspring arising from any radiation doses received. The answer to the second question has a clear dependence on the answer to the first. I discuss both questions briefly.

1. Doses received.

Monitoring of radiation exposures of servicemen involved in the tests was carried out by the British and is reported in the National Radiological Protection Board Report NRPB-R266 (Darby et al, 1993). Apart from air crew involved in cloud sampling missions and a few other persons no significant exposures were received by servicemen attending tests. Taking account of the positions of the observing ships during explosions and the movements of the ships and crews there are no reasons to suppose that NZ servicemen received any significant

exposures. Doses received by servicemen are discussed in more detail in the Appendix.

Epidemiological evidence

In response to claims by navy veterans the New Zealand Government commissioned an epidemiological study conducted by a group at the Wellington Medical School. The report on the health of the New Zealand participants was published in the *British Medical Journal* on 5 May 1990 (Pearce et al, 1990). The study concluded:

Although the numbers are small ... some leukemias, and possibly some other haematological cancers, may have resulted from this programme. There is little evidence of an increased risk for non-haematological cancers, and there is no evidence of an increased risk for causes of death other than cancer.

A report following up the participants for a further 5 years was issued in 1996 (Pearce,1996; Pearce, et al, 1997). The findings were essentially unchanged with no evidence of increased health effects except for the possible excess of haematological cancers. This elevated relative risk was mainly due to 4 deaths from leukemia. The report speculated that radiation may have been a causal factor and that internal exposure from ingestion of foods or neutron radiation may have been involved.

In examining these epidemiological findings it is to be observed that the number of haematological cancers in the study was very small. In regard to the four leukemia cases two points should be noted. Firstly, one of the cases was a chronic lymphocytic leukemia which is a type which has not been demonstrated as being caused by radiation. Secondly, the increased risk of leukemia in the exposed Japanese (Hiroshima and Nagasaki) populations in the 15-29 age group falls to near zero at 25 years after exposure. In the test participants, who were largely within this age range, 3 of the 4 leukemias occurred more than 25 years after the putative time of exposure. Without further evidence, therefore, the epidemiological findings cannot be considered to provide any support for radiation exposure as a cause of the small increase in leukemias.

The much larger British study of British participants at the Australian and Christmas Island tests found no increases in health effects in participants. The NRPB report (p.51) makes similar comments on the NZ study to those in the preceding paragraph. The weaknesses in the New Zealand study conclusions had been earlier flagged in the National Radiation Laboratory publication *Radiation Protection News and Notes* of July 1990 (McEwan, 1990).

Radiological evidence

The National Radiation Laboratory carried out a radiological survey of Christmas Island in 1981 following a request from the British Overseas Development Administration for an independent survey (McEwan et al, 1981). This was in response to a request from the newly independent state of Kiribati.

This study demonstrated that no significant radioactive fallout had been deposited on the island and was consistent with British results of personnel monitoring conducted at the time of the tests. Apart from small groups of British personnel such as aircrew involved in cloud sampling missions, the doses could be considered trivial.

In speculating on possible causes of radiation exposure, the Wellington Medical School reports refer to neutron radiation and possible intake of fallout products. Neither of these are credible sources of significant exposure. The observers were stationed many miles from the detonations, and for megatonne yields, neutron radiation is completely attenuated at distances where blast and thermal (burn) effects do not occur. Further, significant intake of fallout radionuclides is not possible in the absence of accompanying external exposure.

Conclusions

There is no evidence that the participants received any significant radiation exposures, and certainly no exposures that would give rise to any observable health effects.

Apart perhaps from the weak epidemiological evidence for a possible increased risk of leukemias, there is no evidence that the New Zealand test participants suffer from unusual or increased health effects. There is no evidence that the small number of additional leukemias observed have any causal relationship to radiation exposure.

2. **Hereditary effects of radiation exposure**

Authoritative reviews of sources and effects of radiation exposure are provided by the United Nations Scientific Committee on the Effects of Atomic Radiation (UNSCEAR). The last major comprehensive report (over 900 pages) was published in 1993 (UNSCEAR, 1993). Reports on specific topics were published in 1994 and 1996. The 1993 Report has an annex on "Hereditary effects of radiation" and this reviews the evidence from the atomic bombings, the epidemiological study of Sellafield childhood leukemias, and other studies. The summary notes,

Epidemiology has not detected hereditary effects in humans with a statistically significant degree of confidence. The risk estimate based on animals is so small that it would have been surprising to find a statistically significant effect in the end-points studied in Hiroshima and Nagasaki.

A review paper by Doll (1998) states

The intensive study of the children born to the survivors of the Hiroshima and Nagasaki bomb explosions has failed to demonstrate any significantly increased effect at all, and, for several of the postulated indicators, the direction of the trend with dose has been the opposite of what would be expected from damage to parental germ cells, though again not significantly so.

This paper also very briefly considers the Seascale evidence.

Other publications of relevance are "The children of atomic bomb survivors: a genetic study" ed J V Neel and W J Schull (1991), and papers related to the Gardner hypothesis which have references to many other studies: e.g. Little, Wakeford, Charles and Andersson (1996), and Bailey et al (1996).

The clear conclusion from these studies is that no genetic effects have been demonstrated in irradiated human populations and that the risk coefficient for genetic effects in subsequent generations is small. The risk coefficient estimated by UNSCEAR has recently been under review and is being revised downwards (Sankaranarayanan, 1998).

3. Conclusions

I consider therefore that a summary of the two points at issue is

(a) there is no evidence of any radiation exposure of the servicemen in 1957-58 that could give rise to any health effects in the individuals themselves or their offspring, and
(b) no radiation induced hereditary effects have been reported in human populations, even for those exposed to doses giving rise to deterministic effects.

It may therefore be concluded that no hereditary effects in the children of Christmas Island test veterans may be attributed to exposure to radiation arising from the veterans observation of the nuclear tests.

Appendix

Comments on:
A REPORT "MORTALITY AND HEALTH EFFECTS IN PARTICIPANTS OF ATMOSPHERIC NUCLEAR WEAPONS TESTS: A CRITICAL REVIEW" BY CAROL MACDONALD

AND ON

PRESS RELEASES AND WEB SITE POSTINGS OF S R ROFF

1. "Mortality and health effects in participants of atmospheric nuclear weapons tests: a critical review" by Carol MacDonald

This report discusses and reviews a number of epidemiological studies on participants at nuclear tests, but many of these studies have very little relevance to the participation of the New Zealand navy personnel who attended the British tests in the region of Christmas and Malden Islands. The Executive Summary and Comments and Recommendations tend to dismiss film badge dosimetry as unreliable and of no value. This is a sweeping and incorrect generalisation which also ignores other methods of confirming radiation exposures, particularly use of integrating monitoring instruments and ratemeters by which doses at the time were estimated. The accuracy of dose assessment varies with the particular study concerned.

Generally, however, the Summary (pp. 2-3) and the Comments and Recommendations (pp. 4-5) appear to be a valid assessment of *epidemiological* evidence relating to participants in the Christmas Island tests.

Comments on particular points follow.

Accuracy of death certificate diagnoses (p.10). One source of bias not considered by the author is the increased attribution of cancer in cases where it is known or believed that there has been prior exposure to radiation.

Dose reconstruction (p. 11). The report tends to underestimate the reliability of film badge monitoring to measure exposures. External exposures measured by film badges at the time were probably accurate to within about 50% and may have been within about 30% or less for fission product gamma energies. The British policy in monitoring was to monitor largely persons who could be expected to receive some exposure. Where any exposure was problematic, only individuals representative of groups were monitored. The records assembled by the NRPB (in Darby et al, NRPB-R266, 1993) show that of the total 21,358 participants in all British tests only 1716 had non-zero recorded radiation doses. Over half the collective dose was received by men in the RAF. The next largest fraction of the collective dose was received by AWE employees. The permissible annual dose to radiation workers of 50 millisieverts (mSv) was exceeded by only 81 persons across the entire series of British tests (i.e. including those conducted in Australia) and only 483 exceeded 5 mSv. For the Grapple series of tests the higher doses were received by air crew involved in cloud sampling missions and RAF active handling flights.

The quote (on p.12) from the US ACHRE relating to 1953 film badge monitoring is not directly relevant, although a revision of doses from 14 roentgens to 24 rem (240 mSv) is less than a factor of 2. The doses to the participants in this US series (of tower bursts) were clearly much greater than in the Christmas Island tests (of atmospheric bursts). The statements on p.12 of the report in paragraphs 2 and 3 therefore need to be qualified; certainly film dosimetry is not highly accurate, but it is sufficiently accurate to determine doses of a magnitude to be of health concern. Doses of less than 5 mSv, and commonly zero, received by the great majority of participants in the Christmas Island tests have no consequences for health, and can be compared with the 100 to more than 1000 mSv received throughout life by people from natural sources of radiation exposure. The criticisms of Roff in the final paragraph commencing on p.12 are entirely misplaced with regard to the Christmas Is tests.

The references to retrospective biological dosimetry (pp. 13-14) again have no relevance to participants in the British tests. Such methods are only of value for doses of much greater magnitude, greater than 250 mSv.

The discussion under the sub-heading "Extrapolation" indicates a lack of familiarity with the topic, as does the reference to Bertell. No reference is made to the authoritative reports of UNSCEAR and the International Commission on Radiological Protection. Risks of exposure at low doses and dose rates are largely based on studies of persons exposed at higher doses and dose rates, but the evidence is that risk factors recommended by the International Commission on Radiological Protection, derived from UNSCEAR reports, are unlikely to be in error by more than a factor of 3. The values are chosen conservatively because they cannot be assessed directly. For very low doses and dose rates it is not possible to demonstrate any risk. The final paragraph starting on p. 15 seems to be confusing extrapolation to lifetime risk and transfer of risks across populations.

Operation Grapple: Background

This section is largely an outline of epidemiological studies which have been carried out on various groups of participants in nuclear tests. Most of the studies have no direct relevance to the NRPB and Pearce et al studies of participants at the Christmas Is tests. However, it is notable that no excess malignancies were reported in the study of the "boarders" of target ships and "engineering and hull" occupational specialists in the Operation Crossroads study, where doses were much higher than in the British test series.

Roff's criticisms of the methodology of the NRPB study (p. 35) appear to be without foundation. She appears not to understand or accept that the British had good measurements and a good understanding of the doses arising from the testing. Participants in the tests were monitored if there was any likelihood of exposure and the possibility of significant doses to Christmas Is participants being unmonitored or unrecognised is remote. Roff's argument on the control group (top of p.36) is similarly invalid and the reference to the US ACHRE is not relevant. The argument from Roff (following paragraph, p. 36) about the excluded group similarly fails because of the lack of willingness to accept that doses to the group were essentially zero and that this could be assessed with reasonable certainty. The rise in numbers of cancers over the final seven years of follow up is expected from the widely recognised increase in cancer rates with age. The final paragraph in this section again cites Roff, but the quotation and claim of increased risk is not borne out by the epidemiological studies.

New Zealand participants of Operation Grapple (p. 38)

This section outlines the Pearce et al study and follow-up report. This study demonstrated that there was no excess cancer mortality in the participants but it speculated that "some leukemias and haematological cancers may have resulted from participation in the nuclear weapons testing programme", in particular that radiation may have been a causal factor and that internal exposure from ingestion of foods or neutron radiation may have been involved. This speculation is not supportable, as has been noted in this report.

2. Press releases and web site postings of S R Roff

Roff reports on a morbidity (health status) study of members of the British Nuclear Tests Veterans Association and members of the New Zealand Nuclear Test Veterans Association.

These small surveys of volunteer interest groups appear to be subject to considerable bias. The releases report a range of vague symptoms in the small sample populations with claims an increased incidence of a "SAPHO" syndrome with presumed genetic links, but it is not clear whether this is a recognised clinical syndrome. New Zealand participants in the Christmas Island tests received no, or trivial exposures, and no effects attributable to radiation exposure could be expected to be observed. The non-cancerous disease conditions described in the press releases are not recognised as having any association with radiation in the authoritative UNSCEAR reports on "Sources and Effects of Ionizing Radiation".

Some of the questionnaire questions related to health status of offspring. While radiation may cause genetic effects, no effects have been observed in human populations, including the irradiated Japanese groups. New Zealand participants in the Christmas Island tests received no, or trivial exposures, and no genetic effects would be observable in offspring as a consequence.

Roff's evaluations appear speculative and without adequate support.

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Appendix 4

REPORT TO THE ADVISORY COMMITTEE
ON THE HEALTH OF VETERANS' CHILDREN

REPORT ON EPIDEMIOLOGICAL STUDIES OF HEALTH EFFECTS IN CHILDREN OR GRANDCHILDREN OF VIETNAM VETERANS EXPOSED TO AGENT ORANGE AND SIMILAR CHEMICALS

Mark Elwood

May 21, 1999

This report replaces the earlier report of 28 Feb 1999.

TO THE ADVISORY COMMITTEE ON THE HEALTH OF VETERANS' CHILDREN

REPORT ON EPIDEMIOLOGICAL STUDIES OF HEALTH EFFECTS IN CHILDREN OR GRANDCHILDREN OF VIETNAM VETERANS EXPOSED TO AGENT ORANGE AND SIMILAR CHEMICALS

Mark Elwood

May 21, 1999

Contents:

Appendix

1. SCOPE OF REPORT AND METHODS.

This report deals with the first two parts of the 'epidemiologists' brief' noted in the minutes of the meeting of the Advisory Committee on the Health of Veterans' Children, 16th September 1998.

This reads:

9. It was agreed that the methodology for the epidemiological study would be to:
a. examine appropriate and relevant authoritative and peer-reviewed literature;
b. to identify "recognised" conditions by categories of:
   (1). "sufficient evidence of an association";
   (2). "limited/suggestive evidence of an association";
   (3). "inadequate/insufficient evidence to determine whether an association exits", and
   (4). "limited/suggestive evidence of no association".

METHODS

A review of available literature showed that most detailed report on possible effects on children of parental exposure to Agent Orange and similar exposures is from the United States studies of Vietnam veterans. The 1996 report '*Veterans and Agent Orange: Update 1996*' (Institute of Medicine, 1996) was reviewed in detail; this will be referred to as the 'VAO report'. A pre-publication copy of the chapter on reproductive effects of the 1998 update of this report (Institute of Medicine, 1999) has also been reviewed.

Literature searches to identify more recent publications in the scientific literature up to December 1998 were conducted using Medline, and using sources noted in the 1996 report, given in other documents supplied by the Committee, or given in a review of neural tube defects including spina bifida by the present author (Elwood *et al.* 1992).

In addition, opinions were sought on the issue from several international experts on birth defects and related issues, and sources noted by them were assessed.

2. CONCLUSIONS

Possible health effects in the children or grandchildren of Vietnam veterans were classified into the following groups:

(1). "sufficient evidence of an association";
(2). "limited/suggestive evidence of an association";
(3). "inadequate/insufficient evidence to determine whether an association exits",
(4). "limited/suggestive evidence of no association".

1. There is no health outcome affecting the children or grandchildren of Vietnam veterans for which there is "sufficient evidence of an association".

In the American Vietnam studies, the most detailed studies are those of "Ranch Hand" veterans, that is, Air Force personnel who were directly involved in handling Agent Orange and similar materials. Detailed studies of these veterans have been done, with extremely high participation, validation of questionnaire reports against medical records, and the use of a blood test which can assess current dioxin level and by back extrapolation allow an estimate of original dioxin exposure. These studies assess a very large number of health outcomes, and therefore some associations will arise purely by chance, and others may be real associations but may be due to factors other than Vietnam-type exposures. These studies assessed a wide range of effects on reproduction, birth defects, childhood cancer, and other outcomes. Other relevant studies include studies of civilians' exposures to dioxins and similar chemicals through accidental or occupational exposures, and case-control studies of reproductive outcomes in the United States, Canada, Europe, and Australia which assess Vietnam service or dioxin exposure along with other possible risk factors. In the 1996 and 1998 VAO reports, there was no health outcome affecting the children or grandchildren of veterans for which there was "sufficient evidence of an association" with relevant exposures. This conclusion is supported by the current review.

2. For all other health outcomes, apart from spina bifida, there is "inadequate/insufficient evidence to determine whether an association exits".

The distinction between "inadequate/insufficient evidence to determine whether an association exits" and "limited/suggestive evidence of no association" is a judgement relating to the extent and detail of negative evidence, that is, evidence which does not suggest any association between Vietnam-type exposures and a health outcome. The distinction between these categories of conclusions requires a value judgement, which is likely to be variable between different reviewers, and requires a detailed and extensive review of all studies showing no association in their results. Although the main studies have been assessed, to review all the studies is outside the scope of the current review. The 1996 and 1998 VAO reports did not categorise any health outcomes in children in terms of the more stringent negative conclusion, that is "limited/suggestive evidence of no association". That is also the conclusion here.

This categorisation "inadequate/insufficient evidence to determine whether an association exits" can be interpreted in 'common sense' terms as follows. It means that the accumulated scientific evidence, considered with attention to the strengths and weaknesses of the studies available, does not suggest that any of these health outcomes are increased in children or grandchildren of Vietnam veterans: the most reasonable interpretation is that there is no increased risk. However, the studies are limited in size and scope, so it is not possible to 'prove' that there is no increased (or decreased) risk of these health events.

3. For the occurrence of spina bifida in children born to veterans, the data show that the risk may be increased. This is considered as "limited/suggestive evidence of an association".

For spina bifida, the 1996 and 1998 VAO Reports classify the results in terms of "limited/suggestive evidence of an association". The associations seen are based on small numbers of observations, but are seen in two partially independent studies of veterans, the Ranch Hand study, and the CDC Birth Defects study. Associations are also seen in some studies of civilians with occupational exposure to dioxins. An association was also seen in a questionnaire approach used in an earlier aspect of the U.S. veteran's study, but this was not confirmed by medical record validation. In contrast, no association with spina bifida was seen in the Australian veteran's study, in some civilian studies, or in the Seveso study, although all these studies are quite weak. None of these studies assessed the known other factors related to spina bifida, such as folic acid intake. The evidence is weak, and cannot be regarded as definitely establishing causality, but it is reasonable to accept the association as showing a possible causal association.

4. The estimated frequency of spina bifida in births to exposed Vietnam veterans with substantial exposure to dioxin or similar chemicals is from 1 to about 4 per 1000 live births.

This estimate is based on the American experience. Combining all categories of Vietnam service, for the spina bifida study, 454 fathers were identified who reported 1006 conceptions and 792 live births; there were 3 cases of spina bifida, a rate of 3.8 per 1000 live births (95% confidence interval 0 to 8.1 per 1000). These studies included aircrew with higher exposure levels than were likely for most New Zealand personnel. The frequency of spina bifida in the general population of New Zealand is fairly similar to that in the U.S. (around 1 per 1000 births), so these numbers allow some estimation of the expected number of similarly defined events in New Zealand veterans.

5. A recent (1998) Australian questionnaire study of veterans, available as a draft report, has been reviewed but found not to be helpful.

In its current form, this report (Commonwealth Department of Veterans' Affairs, 1998) has serious methodological problems, and the results are likely to be greatly affected by recall bias. Even in the American studies, which had much more rigorous methodology, results of

questionnaire approaches were found to be unreliable unless validated by direct assessment of medical records. The assessment is included as Appendix 1 of this report.

6. Valid conclusions on these issues can be confirmed only from studies with unbiased documentation of health outcomes in all births, and ideally in all known conceptions, to defined groups of veterans, with the use of appropriate comparison groups. Such studies require a high response rate, assessment of medical records or clinical examinations to verify health conditions, attention to methods to minimise bias in exposure recall, and attention to the likely effects of other risk factors.

Questionnaires alone are insufficient. The difficulties with questionnaire studies seen in the U.S. and Australia have implications for the New Zealand questionnaire study currently being conducted, and make it clear that any interpretation of those results needs to be extremely cautious.

3. SCOPE OF THE U.S. 'VETERANS AND AGENT ORANGE' REPORTS

In the current report, emphasis has been given to the relevant sections of the "Veterans and Agent Orange Update, 1996" (Institute of Medicine, 1996) and to the 1998 update (Institute of Medicine, 1999).

Scope

This is a "comprehensive review and evaluation of scientific and medical information regarding the health effects of exposure to Agent Orange, other herbicides used in Vietnam, and the various chemical components of these herbicides, including dioxin", carried out by the Institute of Medicine (IOM) of the National Academy of Sciences (NAS) in the United States and authorised by Congress under the "Agent Orange Act of 1991" (page 1).

Under this law, the NAS is to conduct subsequent reviews at least every two years for a period of ten years from the date of the first report, which was published in 1994 (Institute of Medicine, 1994). The 1998 update is now close to publication. A pre-publication draft of the relevant section was supplied by Dr David Butler of the Institute of Medicine in United States, and has been reviewed.

The IOM was asked to determine

1. whether a statistical association with herbicide exposure exists, taking into account the strength of the scientific evidence and the appropriateness of the statistical and epidemiological methods used to detect the association,
2. the increased risk of the disease amongst those exposed to herbicides during Vietnam service, and
3. whether there is a plausible biological mechanism or other evidence of a causal relationship between herbicide exposure and the disease" (1996 update, p. 1).

Methods

On page 5 (1996 update) it is stated that "consistent with the mandate of Public Law 102-4, the distinctions between categories are based on 'statistical association', not on causality, as is common in scientific reviews. Thus, standard criteria used in epidemiology for assessing causality, do not strictly apply". This implies that the criteria used in this document are somewhat less stringent than the general criteria used to assess causality in epidemiology, as statistical association is merely one of several criteria used in such assessments (Hill, 1971; Elwood, 1998). This more stringent range of criteria used in epidemiological assessment of causal relationships has also been accepted in legal judgements, such as that relating to Sellafield (Wakeford, 1998). Thus the use of the VAO results would tend to be generous, in terms of recognising a condition as potentially related to hazardous exposures.

Comments

The VAO reviews have been carried out by a reputable and independent scientific group. The reports include detailed discussions, not only of the specific studies related to Vietnam veterans, but of other relevant studies related to exposure to similar agents, for example, studies of people occupationally exposed to dioxins. It is appropriate to give great weight to these reports in reviewing the available literature on this topic.

The reports are authoritative, independent, and detailed. The resources that have gone into this document are very substantial. The terms of reference ensure that there is adequate attention paid to the separation of a potentially causative relationship from a coincidental finding, and the report discusses the relevant methodological issues in detail.

The categories of association used in conclusions.

The criteria for the four categories of association, noted above, are defined in terms of associations, and are therefore weaker than the generally used epidemiological criteria for such assessments which seek to distinguish cause-and-effect relationships from mere association. However, despite this definition, the detailed reviews presented in the VAO reports assess studies in terms of causal reasoning, looking at consistency, dose-response, bias in observations, statistical significance, biological mechanisms, and other features in forming conclusions. Therefore, the VAO process, as applied, is closer to an assessment of causality than the definitions of the four categories of conclusions would suggest.

The 1998 VAO report (Institute of Medicine, 1999) expands on the interpretation of these four categories. The following material is taken from the executive summary of the 1998 report.

'Sufficient Evidence of an Association': "That is, a positive association has been observed between herbicides and the outcome in studies in which chance, bias, and confounding could be ruled out with reasonable confidence. For example, if several small studies that are free from bias and confounding show an association that is consistent in magnitude and direction, there may be sufficient evidence for an association." There is sufficient evidence of an association between exposure to herbicides and the following health outcomes (in exposed veterans themselves, not in their children): soft-tissue sarcoma, non-Hodgkin's lymphoma, Hodgkin's disease, and chloracne.

'Limited/Suggestive Evidence of an Association': "Evidence is suggestive of an association between herbicides and the outcome but is limited because chance, bias, and confounding could not be ruled out with confidence. For example, at least one high-quality study shows a positive association, but the results of other studies are inconsistent." There is limited/suggestive evidence of an association between exposure to herbicides and the following health outcomes (in exposed veterans themselves, not in their children): respiratory cancers (lung, larynx, trachea); prostate cancer; multiple myeloma; acute and subacute transient peripheral neuropathy; and porphyria cutanea tarda; and (as discussed below) spina bifida in the children of veterans.

'Inadequate/Insufficient Evidence to Determine Whether an Association Exists': "The available studies are of insufficient quality, consistency, or statistical power to permit a conclusion regarding the presence or absence of an association. For example, studies fail to control for confounding, have inadequate exposure assessment, or fail to address latency." The report lists 22 conditions under this heading, including spontaneous abortion, birth defects (other than spina bifida), neonatal/infant death and stillbirths, low birthweight, and childhood cancer in offspring.

'Limited/Suggestive Evidence of No Association': "Several adequate studies, covering the full range of levels of exposure that human beings are known to encounter, are mutually consistent in not showing a positive association between exposure to herbicides and the outcome at any level of exposure. A conclusion of "no association" is inevitably limited to the conditions, level of exposure, and length of observation covered by the available studies. In addition, the possibility of a very small elevation in risk at the levels of exposure studied can never be excluded." There is limited/suggestive evidence of *no* association between exposure to herbicides and the following health outcomes (in exposed veterans themselves, not in their children): gastrointestinal tumours (stomach cancer, pancreatic cancer, colon cancer, and rectal cancer); brain tumours.

Herbicides used in Vietnam

Agent Orange, named from the colour identification bands on the drums and tanks containing it, is a 1:1 mixture of 2,4,5-T (2,4,5-trichlorophenoxyacetic acid) and 2,4-D (2,4-dichlorophenoxyacetic acid). 2,4,5-T is usually contaminated by about 2 ppm of TCDD (2,3,7,8-tetrachlorodibenzo-*p*-dioxin), 'one of the most toxic man-made chemicals' (Kramárová *et al.* 1998). Agent Orange and related herbicides such as Agent White (a 4:1 mixture of 2,4-D and pichloram (4-amino-3,5,6-trichloropicolinic acid)) and Agent Blue (a mixture of dimethyl arsinic acid and sodium dimethylarsenate) were used as a defoliate in the Vietnam conflict (Grassman *et al.* 1998; O'Keefe and Smith, 1994).

4. SUMMARY OF RESULTS ON SPINA BIFIDA

The conclusion reached by the Veterans and Agent Orange 1996 and 1998 reports (Institute of Medicine, 1996; Institute of Medicine, 1999) is that there is "limited/suggestive evidence of an association" between herbicide exposures and spina bifida. This is based on the following evidence.

1. Small, uninformative, studies

The VAO 1996 report notes several occupational exposures of workers in dioxin production plants, although these do not give results specific to spina bifida. A study related to the Dow chemical plant found no increased risk of total abnormalities (Townsend *et al.* 1982), and two studies of the plant in Nitro found no significant excesses (Moses *et al.* 1984; Suskind and Hertzberg, 1984). A study of 245-T sprayers in New Zealand found a non-significant but slightly elevated risk of congenital anomalies, based on self-administered questionnaires with no validation (Smith *et al.* 1982).

A large number of environmental studies relating herbicide exposure to birth defect occurrence are quoted, but it is noted that their interpretation is difficult, because of inconsistency in results, and the fact that these studies were mainly ecological studies (a very weak type of study) with limited statistical power, and lacking validation of the birth defects. The 1996 review notes a study carried out in Vietnam of offspring to mothers who lived in a village which had been sprayed, showing a strong increased risk of birth defects based on 81 occurrences (odds ratio 3.8, limits 1.1-13.1), but notes that there was little information as to how the birth defects were diagnosed, what types were detected, how the case and control groups were derived, and how the data were collected (Phuong *et al.* 1989). Other Vietnam civilian studies have been reviewed in a further publication (Constable and Hatch, 1985), but these studies also suffer from poor reporting and many methodological problems

2. The Vietnam Experience Study

The Vietnam Experience Study, conducted by the Centres for Disease Control (Centers for Disease Control, 1988; Centers for Disease Control, 1989) involved a comparison of Vietnam veterans with veterans who did not serve in Vietnam, using first a telephone interview, and then assessment of hospital records.

The *interview study* showed an increased risk for all birth defects (relative risk 1.3, 95% confidence limits 1.2-1.4), which included an increase for nervous system defects (relative risk 2.3, limits 1.2-4.5). The increases in central nervous system defects were seen independently for hydrocephalus, and spina bifida. In addition, there were excesses of defects of the ear, face and neck; skin; and musculoskeletal defects. Some of the latter groups reflected minor defects, which would tend not to be reliably diagnosed or reported. There were also excesses seen for hypospadias and for multiple defects. There was a dose-response gradient seen comparing the occurrence of total defects with a self-reported estimate of herbicide exposure.

There were then two sub-studies using hospital records to identify birth defects. In the *general birth defect study* (GBDS), the occurrence of birth defects in hospital records was compared between Vietnam and non-Vietnam veterans. There was no difference in the frequency of total birth defects, a slight but non-significant excess for major birth defects (relative risk 1.2, limits 0.8-1.9), and analysis by specific defect showed an excess only for digestive system defects. Thus the results based on hospital record reviews did not confirm the results based on interview.

The second sub-study assessed medical records specifically for central nervous system defects, including stillbirths. This however did not lead to a formal analysis because the numbers of defects dealt with were very small.

3. The CDC Birth Defect Study

The second major relevant study was the CDC Birth Defect Study (Erickson *et al.* 1984). This showed no increase in total major birth defects in relationship to Vietnam service, and no trend in the risk of birth defects with estimated Agent Orange exposure based on both medical records and self-reports. For spina bifida, while overall there was no excess in Vietnam veterans (odds ratio 1.1), there was an increasing trend with estimated Agent Orange exposure, the risks from low to high levels of exposure being 1.2, 1.5, 1.8, 2.2, and 2.7, all of these being significantly increased compared to the lowest exposure group. A similar pattern was seen with cleft lip and/or cleft palate. There was however no association or trend for anencephalus, which generally occurs with similar patterns as spina bifida. The response rate in this study was also low, around 56%, and the interviews occurred up to 14 years after the relevant births.

4. The Ranch Hands study: reproductive outcomes in Ranch Hand Veterans

This study (Wolfe *et al.* 1995) compares Ranch Hand veterans with the Air Force comparison cohort in terms of adverse reproductive outcomes, and was published in 1994, and forms the main grounds for the 1996 VAO report's conclusions.

The authors state "We found no meaningful elevation in risk for spontaneous abortion or stillbirth. In analyses of birth defects, we found elevations in risk in some organ system categories, which, after review of the clinical descriptions, were found to be not biologically meaningful. There was an increase in nervous system defects in Ranch Hand children with increased paternal dioxin, but it was based on sparse data. We found no indication of increased birth defect severity, delays in development, or hyperkinetic syndrome with paternal dioxin. These data provide little or no support for the theory that paternal exposure to Agent Orange and its dioxin contaminant is associated with adverse reproductive outcomes" (p. 17).

The study compares 1,098 Air Force veterans who handled and sprayed dioxin-containing herbicides from 1962-71, and the comparison group is 1,549 Air Force veterans who served in south-east Asia at the same time without such exposure. Physical examinations and

questionnaires were administered in 1982, 1985, 1987 and 1992, and additional examinations planned for 1997 and 2002.

Reproductive experiences were first assessed in a 1984 report, based on reporting by the mothers without verification. In 1985, collection of medical records on 9921 conceptions and 8100 births commenced. The authors verified the existence, lineage and medical history to the age of 18 of 9,891 of the reported conceptions (99.7%) and 8,090 of the reported births (99.9%).

The veterans, their wives, and other partners were asked about birth defect and mortality status of children in 1982, 1985, and 1987, and to provide access to medical records. Blood was collected for dioxin assay in 1987, and was given by 94% of Ranch Hands and 93% of comparison veterans who were physically examined at that time.

This study is based on 932 Ranch Hands and 1202 comparison subjects with serum dioxin specimens analysed by January 1990. Serum results below the limits of quantifiability, or due to laboratory errors, or beyond the upper threshold for background exposure in controls were excluded, leaving 872 Ranch Hands and 1,036 comparison subjects.

All conceptions were verified by medical records and birth and death certificates. All retrieved records were independently reviewed for the identification and classification of anomalies and morbid conditions by two experienced record coders, blinded to the fathers' exposure status and dioxin levels. A clinical geneticist, blinded to exposure status, independently reviewed all anomalies.

All analyses were adjusted for father's race, mother's smoking during pregnancy, mother's drinking during pregnancy, mother's and father's age at the child's birth, and father's military occupation (officer, enlisted flyer, enlisted non-flyer). Data on spontaneous abortions were also adjusted for occurrence of spontaneous abortions before south-east Asia service.

As in other Ranch Hand studies, the Ranch Hands are divided into three groups with (a) background, (b) low, and (c) high dioxin levels. The key criterion for an association is a statistically significant excess risk which shows a logical dose-response pattern in relationship to dioxin level. However, it is difficult to interpret results based on small numbers.

The only outcomes with reasonable numbers were spontaneous abortions, and total abnormalities. Each of these showed no excess in the background or in the high dioxin group compared to the comparison group, but a marginally significant increase, relative risk 1.3, in the low dioxin group compared to the comparison group. Total major defects were also elevated in the low exposure Ranch Hand group, relative risk 1.7 (limits 1.1-2.7); specific delays in development were also elevated in the low exposure group (RR 1.5, limits 1.0-2.3), but neither were increased in the high exposure group.

The prime difficulty is that although this is the most detailed and largest study of birth defects in the Ranch Hand group, the results are based on very small numbers. For abnormalities of the eye, the ear, face and neck, and the urinary system, there were elevated risks in the high exposure category, although none were significant. For several other classifications of

defects, there were one or two elevations, some of which are of marginal statistical significance, but these occurred in the background or low dioxin groups. In the text, the authors point out that even within the groups given, the specific defects are very varied, which they argue makes a causal relationship less likely.

In regard to central nervous system defects, they state that "although the number of children with nervous system anomalies was too small to be analysed, we noted an increasing rate with increasing paternal dioxin level". This conclusion was based on the findings for anencephalus and spina bifida, where there were 0 cases in the comparison group (out of 981 liveborn infants), 0 cases in the background level exposed group (out of 283 births), 2 cases in low exposure Ranch Hands (241 births), and 2 in the high exposure group (of 268 births); Table 5 of the paper. For all nervous system defects (as given in the text on page 20), there were 3 in the comparison, 0 in the background, 2 in the low, and 3 in the high exposure group. The 3 in the comparison group comprised one each of hydrocephalus, macrocephaly, and microcephaly.

The authors conclude that this study shows an increase in neural tube defects, consistent with earlier observations from the same group of veterans, despite the small numbers of these defects. The results "provide no definitive evidence that paternal dioxin exposure causes birth defects" but "do not eliminate the possibility that particular subgroups of anomalies that we were unable to examine owing to small numbers might be associated with paternal dioxin exposure" (p. 21).

In discussion, the authors quote two studies of reproductive outcomes following exposure to dioxins in male rats. One study (reported as a technical report) showed no effect on mating behaviour, litter size, or birth defects rates. The second study (published) showed a decrease in mating index, increase in sterility, and normal pregnancy index. They also quote four studies of the effects of dioxin in cultures derived from foetal animal tissue, which shows effects on neural, palate and kidney tissues, but note that the applicability of these results to humans is debatable.

The paper was published with an accompanying editorial (Lindbohm, 1995). It notes "so far, there is no established male exposure proven to influence pregnancy outcome in humans, despite several potential mechanisms that have been proposed" (p. 4). The writer notes that TCDD (2,3,7,8-tetrachlorodibenzo-*p*-dioxin) did not induce pregnancy abnormalities in animals when male rodents were exposed before mating in a 1987 study. In animals, higher dosage of TCDD has caused decreased testis weight, abnormal testicular morphology, decreased spermatogenesis, and reduced fertility. Lower sperm concentrations and fewer normal sperm cells were reported amongst Vietnam veterans, but the differences could not be attributed to herbicide exposure. For human studies, some studies noted an increase in spontaneous abortion after Agent Orange exposure in pregnancies not verified by medical record review, but no excess when verified data were used. The author concludes that these results "indicate no large adverse effect of paternal dioxin exposure. The data are among the best to date on this question. Nevertheless, the book is not yet closed on the question of whether paternal dioxin exposure harms offspring" (p. 5).

5. Other smaller studies

A case-control study in Boston (Aschengrau and Monson, 1990) assessed the father's military service from military records, and showed a small non-significant increase in all congenital defects related to Vietnam service (odds ratio 1.3, limits 0.9-1.9). Increases were seen for central nervous system defects, although these were based on small numbers and were non-significant.

Several other smaller studies are also noted in the 1996 VAO report, which do not add substantial evidence.

6. Australian study

The Australian study of birth defects (Donovan *et al.* 1984) showed no increase in total birth defects in Vietnam veterans compared to other men who were in army service but did not serve in Vietnam (odds ratio 1.0, limits 0.8-1.3), and analysis by specific defect did not show any increase for central nervous system defects.

7. New information in the 1998 VAO report

The 1998 VAO report reviews four more recent studies, all of civilian populations exposed to pesticides or herbicides which may contain dioxins or related compounds. These are: a study of birth defects and other reproductive outcomes in the offspring of fathers employed in sawmills in British Columbia (chlorophenate wood preservatives had been used in the sawmills; although TCDD was not used, other dioxins were present) (Dimich-Ward *et al.* 1996); a study of birth defects in the offspring of male pesticide applicators in Minnesota (Garry *et al.* 1996); a case-control study of spina bifida in regard to paternal occupation in the Netherlands, assessing agricultural work and pesticide exposure (Blatter *et al.* 1997); and a record linkage study of birth defects in the offspring of farmers in Norway (Kristensen *et al.* 1997).

Three of these studies (in British Columbia, the Netherlands, and Norway) showed positive associations between some measure of pesticide or herbicide use and the occurrence of neural tube defects in the offspring of male workers; the other study (in Minnesota) showed no association. All of the studies have only small numbers of cases, and in only one study (Norway) is the main association statistically significant. However in total these studies support the concept that exposure to pesticides or herbicides which may contain dioxins increases the risk of neural tube defects, although other explanations, such as dietary effects, cannot be excluded.

The VAO 1998 report presents a synthesis of this work, with the conclusion that "limited / suggestive evidence for an increased risk of spina bifida amongst offspring of Vietnam veterans" exists. The reports notes, however, that " concerns remain, including the control of confounding, exposure determination, statistical imprecision, and isolation of exposure to specific herbicides and TCDD."

Rationale behind the VAO conclusions

The Veterans and Agent Orange 1996 inclusion of spina bifida in the "limited/suggestive evidence" category is based partially on the Ranch Hand study, which in turn is based on the finding of only two cases of spina bifida in the high exposure group, one in the low exposure group, and zero in the comparison or background groups. This result is clearly not statistically significant. The other major evidence is from the CDC Birth Defects study, again based on very small numbers, which showed no overall significant excess, but a pattern of exposure with a positive trend between occurrence of the defect and estimated exposure. The Vietnam Experience Study also shows some excess, but this is based on questionnaire data and the follow up studies based on hospital records do not confirm the relationship.

The summarisation of the 1996 report is that "thus all three epidemiological studies (Ranch Hand, VES, CDC Birth Defects study) suggest an association between herbicide exposure and an increased risk of spina bifida in offspring. Although the studies were judged to be of relatively high quality, they suffer from methodological limitations, including possible recall bias, non-response bias, small sample size, and misclassification of exposure. In addition, the failure to find a similar association with anencephalus, an embryologically related defect, is of concern" (p 296).

The 1998 report concludes that the occupational studies reviewed above provide some additional support for the association of herbicide exposure with spina bifida, although "concerns remain, including the control of confounding, exposure determination, statistical imprecision, and isolation of exposure to specific herbicides and TCDD."

Lack of control for other risk factors for spina bifida

The Veterans and Agent Orange Reports do not discuss what is known in general about the epidemiology of spina bifida, despite this being one of the few major defects in which a clear causal factor has been definitively identified.

The major cause of spina bifida is known to be folic acid deficiency (Elwood *et al.* 1992). This has been shown by observational, case-control and cohort studies, and most clearly by an international multicentre randomised trial which showed a 70% reduction in the recurrence rate of spina bifida after adding 4 mg folic acid daily to the maternal diet, from before conception (MRC (Medical Research Council) Vitamin Study Group, 1991). Another randomised trial has shown a reduction in first occurrences of the defect with multivitamin supplementation (Czeizel and Dudas, 1992). Dietary supplementation with folic acid is now recommended for all women planning a pregnancy, in New Zealand and in many other countries (Wald *et al.* 1998). Rules on the fortification of flour and cereals with folic acid have been modified to encourage a greater intake. The factor increasing risk of spina bifida is a functional deficiency of folic acid in the mother during very early pregnancy: this is likely to be a combination of low intake, low absorption, and genetic predisposition by mothers having abnormalities in one or more genes which control enzymes involved in the

metabolism of folic acid and vitamin B12, and in the synthesis of components of DNA (Kirke *et al.* 1996).

The epidemiology of spina bifida shows a large number of studies in which some occupational association was seen. For example, an extensive review (Little and Elwood, 1992) (p. 474), lists occupational situations for which there are at least two studies showing statistically significant increases in central nervous system malformations or neural tube defects. These include, for paternal occupations, paper manufacture, painting occupations, transport and communication, engineering, and armed forces occupation in the context of British studies; and for maternal exposures, occupations involving textiles and clothing, sales, or industry construction and labouring. The British data on the armed forces occupation relates to two studies: one of births with neural tube defects occurring during 1965-72, and the second relating to neural tube defects in births in Britain during the period 1974-79. Also relevant is a strong social class difference for neural tube defects, with substantially higher rates in less affluent parents (Little and Elwood, 1992). These occupational and social variations, and many other variations with, for example, maternal parity and age, may relate to folic acid metabolism, or may indicate other effects.

The studies including the Vietnam Veterans and Ranch Hand studies, which the VAO uses to conclude that a possible association exists between herbicide exposures and spina bifida, do not take into account any dietary variables, although they do have some control for some other potential risk factors. So the associations seen with spina bifida may be due to other factors, such as differences in diet, rather than due to chemical exposures.

Spina bifida: general comments

Spina bifida occurs in New Zealand at a rate of approximately one per thousand live births. In recent years, a substantial but unknown proportion of cases will have been diagnosed antenatally by ultrasound or measurement of AFP (alpha-fetoprotein) levels, and mothers offered induced abortion. The severity of spina bifida varies considerably, from being a severe permanent disability to the existence of minor and even asymptomatic subtypes identifiable only on spinal x-ray. Anencephalus is a closely related defect with a generally similar epidemiology, and a similar frequency, although as it is incompatible with life, all cases resulting in abortion, stillbirth, or early infant death. Anencephalus and spina bifida together, along with some rarer abnormalities, are referred to as 'neural tube defects'. The evidence to associate anencephalus with Vietnam exposures was inadequate in the data reviewed by VAO, but on general grounds, there might be logic to accept a potential association with anencephalus on the basis of general similarity of these conditions.

The expected frequency is around 1 in 1000 births. Approximately 3400 Vietnam veterans have been identified, and if there were a similar number of births (in the U.S. Ranch Hander Study, interviews with 1174 ranch handers produced information on 919 live births, delivered after Vietnam service), we would expect some 3 to 4 cases of spina bifida at normal rates. The U.S. studies suggest a risk of up to 4 per 1000 in births to veterans with substantial exposures; most of the other studies showing an increased risk give rates of around 2 per 1000. It would be expected that perhaps half of cases of spina bifida occurring would present as spontaneous or induced abortion, stillbirth, or infant death.

Given this low expected frequency, any study within the New Zealand Vietnam group, such as comparing service personnel with particularly high exposures with others, would have insufficient statistical power to reach any substantive conclusion as to whether the occurrence of spina bifida varied with estimated exposure dosage.

5. SUMMARY OF RESULTS ON INFANT DEATHS IN PRE-TERM BABIES

In a further Ranch Hand study published in 1998 (Michalek *et al.* 1998), the authors assessed intrauterine growth retardation, pre-term birth, and infant death amongst children conceived during or after the father's service in south east Asia. Paternal dioxin levels were measured in 1987 or 1992 and extrapolated back to the time of conception of the child. A comparison between the comparison group and background, low, and high exposure Ranch Hand categories was made. This study gives dioxin levels and occupation for the four groups (Table 4 in the paper); the median paternal dioxin level was 3.7 ppt (parts per trillion body burden) in the comparison group, and 5.6, 39.0, and 153.4 in the background, low, and high Ranch Hand groups respectively.

There was no excess of intra-uterine growth retardation in any Ranch Hand group. For pre-term birth, there were non-significant excesses in the background and high dioxin groups, and a non-significant reduction in risk in the low exposure group. For infant death, there were excess risks in all three Ranch Hand groups, significant in the background and high groups, the relative risks and 95% confidence limits being background 3.2 (1.0-10.3), low dioxin 1.5 (0.3-7.5) and high dioxin 4.5 (1.5-14.0), the latter being based on six cases. Most of these deaths were in babies born before 37 weeks' gestation (pre-term babies). The gender distribution of all the children was similar to that expected, with a slight deficit of females amongst the highest exposure group (47 % being female).

To explore this further, Ranch Hand veterans in the low and high dioxin categories were divided further into quintiles of initial dioxin level, and most infant deaths (five of eight) were seen in the second highest quintile. The authors note that "it appears that most Ranch Hand veterans with background levels were probably unexposed or received a minimal exposure to herbicides in Vietnam". The authors' final conclusion is "this pattern implies that these outcomes may not be related to paternal dioxin level" on the basis of the lack of a clear dose-response across the categories. However given the numbers of events, and the wide confidence limits, to expect a regular dose-response would seem ambitious. Without that consideration, this study indicates an excess infant death rate, primarily in short gestation low birth weight infants, which is seen comparing Ranch Hand veterans with the comparison group, and shows a partial dose-response effect giving highest death rates in the highest exposure group. The excess death risk is of deaths occurring amongst premature babies.

These results can be summarised as follows. In the comparison group, of 1,223 births, 4.4% were premature (54), and of these, two died (3.7%). In the low and high dioxin exposure categories combined, the rate of prematurity was similar (22 of 536 births, 4.1%), but of these 22 premature babies, five died in infancy (23%). However a similar pattern was seen in the background dioxin level Ranch Hand veterans, where the prematurity rate was 20 out of 323 (6.2%), and of those 20, five died in infancy (25%). Thus the authors conclude that there is an excess infant death rate in the Ranch Hand veterans' children, concentrated amongst premature births, but that this is seen both in Ranch Hand veterans with background dioxin exposures, as well as in those with likely moderate or high exposures.

In their 1998 report, the VAO group reviews this study extensively, pointing out the limitations described above, and noting that the study is inconclusive but "nevertheless, the

findings remain intriguing and cannot be dismissed." They note that the association was not consistently related to level of exposure, and was also found for the period prior to service in south-east Asia. They note only one other relevant study, of sawmill workers in British Columbia (Dimich-Ward *et al.* 1996), which found no association with either stillbirths or infant deaths. In their synthesis statement, the VAO 1998 group concludes that the evidence remains inadequate.

So in conclusion, there is "inadequate or insufficient evidence to determine whether an association exists" between exposure to the herbicides considered in this report and stillbirth, neonatal death, and infant death.

6. REPRODUCTIVE HEALTH OF VETERANS.

The Veterans and Agent Orange Reports, 1996 and 1998 conclude that there is "inadequate or insufficient evidence" to relate herbicide exposure in Vietnam to altered sperm parameters, infertility, spontaneous abortion, or stillbirths (Institute of Medicine, 1996; Institute of Medicine, 1999). The available results are variable and inconsistent.

A study of Ranch Hand subjects (Henriksen *et al.* 1996) compared to Air Force veterans not involved with spraying herbicides, matched by date of birth, race and military occupation. It shows no association between dioxin levels and testosterone, FSH (follicular stimulating hormone), LH (luteinising hormone), testicular abnormalities, sperm count, sperm abnormalities, or testicular volume in Ranch Hand subjects. The authors report "We found no consistent or meaningful association between serum dioxin levels and any of these outcome variables". The first four outcomes noted above were assessed four times, in 1982, 1985, 1987 and 1992, so there are many comparisons. Some do show associations but there is no consistent pattern or dose-response comparing Ranch Hands with background, low, and high exposures. For abnormal sperm, and low sperm count, there were no exposed Ranch Hands who showed any higher frequency of these conditions. The authors note a study of industrial workers exposed to dioxins (Egeland *et al.* 1994) who had higher dioxin body burdens than the current levels for the Ranch Hands, and had shown high FSH and LH levels, and a greater frequency of low testosterone, in the workers with the highest dioxin levels. The authors conclude that "if adverse effects exist, the Ranch Hand exposure in south east Asia was insufficient to produce detectable associations comparable with those seen in industrial workers with heavy exposure".

A study of the British Columbia sawmill workers (Heacock *et al.* 1998) found reduced fertility rates among the workers, but this was not related to the extent of exposure to the main chemicals used, chlorophenates.

7. OTHER BIRTH DEFECTS AND PERINATAL CONDITIONS.

Studies of Vietnam exposures

The Veterans and Agent Orange Reports, 1996 and 1998 concludes that there is "inadequate or insufficient evidence" to support links with other types of birth defect. There were some instances in individual studies of excesses of other birth defects, although these were inconsistent (Institute of Medicine, 1996; Institute of Medicine, 1999).

The main study (Wolfe *et al.* 1995) comparing Ranch Hand veterans with the Air Force comparison cohort in terms of adverse reproductive outcomes, which forms the main grounds for the 1996 report's conclusions, has been reviewed above. Apart from the association with spina bifida, the other conclusions were negative. As noted above, although this is the most detailed and largest study of birth defects in the Ranch Hand group, the results are based on very small numbers. For abnormalities of the eye, the ear, the face and neck, and the urinary system, there were elevated risks in the high exposure category, although none was significant. For several other classifications of defects, there were one or two elevations in risk, some of which are of marginal statistical significance, but these occurred in the background or low dioxin groups. In the text, the authors point out that even within the groups given, the specific defects are very varied, which they argue makes a causal relationship less likely.

Other studies of congenital defects in regard to pesticides and similar occupational exposures

A study (Bertazzi *et al.* 1998) in children born after the accident in Seveso, Italy, which released substantial amounts of TCDD (2,3,7,8-tetrachlorodibenzo-*p*-dioxin) shows no evidence of chromosomal abnormalities or birth defects. Infants born between 1977 and 1982 were examined for the presence of congenital malformations. There were some 187 cases of chloracne (a skin condition), of which 164 were in children. In regard to reproductive effects, it is noted that "several attempts were made to evaluate the possible increased risk of spontaneous abortions by using different sources of information, but the results were inconclusive. Comparison of cytogenetic findings on induced abortions in 19 exposed and 16 non-exposed women yielded inconclusive results. A higher frequency of chromosomal aberration in foetal tissue from TCDD-exposed women was found, but potential problems with variability in the cell culture process were noted", and "no consistent evidence emerged of chromosomal effects associated with TCDD exposure. The presence of congenital anomalies was evaluated in 34 subjects, 30 with induced abortions and 4 with spontaneous abortions. Direct examination and histologic studies of the embryos failed to demonstrate any gross developmental abnormalities" (p. 627-8).

A change in the sex ratio, with an excess of female offspring, was observed between 1977 and 1984 among children born to parents with high TCDD serum concentrations in 1976 (Bertazzi *et al.* 1998). Suggested explanations for this change are dioxin-related

modifications of the hormonal balance or an effect on genes controlling gender, but the change in sex ratio remains unexplained. There was no such change in the births to Ranch Hand veterans (Michalek *et al.* 1998), or in births after dioxin exposures in Taiwan (Rogan *et al.* 1999).

Sever *et al.* (1997) review the reproductive and developmental effects of occupational pesticide exposure. Under male reproductive toxicity, the effects of DBCP (dibromochloropropane), Kepone (chlordecone), and EDB (ethylene dibromide) are discussed, showing that "the reproductive toxicity of three pesticides has been established for men" in terms of effects on spermatogenesis. The most relevant section is that on developmental effects due to paternal occupational exposure. Studies are noted in civilian populations which relate congenital malformations to the father's exposure to pesticides, reporting excesses of a range of birth defects. These authors review studies in British Columbia and India which showed associations between several disparate defects and pesticides, concluding that the British Columbia study was based on a very large number of comparisons, and that in the Indian study, the prevalence of malformations in the unexposed group was abnormally low. They also note a case-control study of anencephalus in Texas which showed non-significant increased risks. A cohort study of certified agricultural pesticide users in Minnesota showed a modestly increased risk of total abnormalities, which was statistically significant, relative risk 1.4, limits 1.2-1.7. Excesses were seen in several categories of defects. In addition, the Agent Orange studies are reviewed in detail. The conclusion is that "there is increasing evidence for reproductive and developmental effects of both maternal and paternal exposures. Areas of particular concern include infertility and time to pregnancy, spontaneous abortion, neural tube defects, and limb reduction defects. The continuing unresolved questions about the effects of Agent Orange and dioxin exposure have important public health policy implications" (page 322).

In the recent studies reviewed in the 1998 VAO report, associations with chlorophenate exposure were seen in British Columbia for cataracts, anencephalus, and anomalies of the genital organs (Dimich-Ward *et al.* 1996). In Minnesota (Garry *et al.* 1996), births to pesticide applicators showed increased risks of circulatory/respiratory, gastrointestinal, urogenital and musculoskeletal, and other defects, but not of nervous system defects. In Norway (Kristensen *et al.* 1997), associations with hydrocephalus, cryptorchidism, hypospadias, and limb reduction defects were seen, with no association for anencephalus. In all these studies, many types of defects and several measures of exposure were used, giving a large number of possible associations to be assessed, so some positive findings will occur by chance. The lack of consistency between the various studies, in contrast to the partial consistency seen for spina bifida, is a major reason while the category of "inadequate or insufficient evidence" is appropriate for defects other than spina bifida.

A recent U.S. study (Cowan *et al.* 1997) showed no increase in birth defects in the children of veterans of the Gulf War of 1990-91, the rates of any birth defect in live births being 7.45 percent, and of severe defects being 1.85 percent.

Reviews of animal experimental work related to dioxin exposures

A 1993 workshop on perinatal exposure to dioxin-like compounds and reproductive effects has been reported (Eskenazi and Kimmel, 1995). The authors report that in male animals exposed postnatally, dioxins alter testis weight, testicular morphology, spermatogenesis and fertility. Female animals have shown decreased fertility and also an increase in endometriosis. Exposures prior to conception and/or in early pregnancy produce offspring with reduced birthweight, and the authors note that these findings are similar to the effects in pregnant women who consumed rice oil containing TCDD, whose offspring showed reduced birthweight and effects on ectodermal organs including skin, nails and meibomian glands. Various reproductive deformities or changes in reproductive behaviour have been noted in animals exposed *in utero.*
No results are presented for studies of humans, although studies of groups who may consume contaminated fish (anglers in New York State and Inuit in arctic Canada) are described as in progress. The mechanism of these actions of TCDD is unknown, and the association with the Ah receptor does not apply to all actions.

The overall summary of the same 1993 workshop includes a detailed appendix listing a large number of animal studies (Lindström *et al.* 1995). None of these deals with effects on the offspring of male animals exposed prior to conception.

While not concerned with dioxins, Hales *et al.* (1992) reported a transgenerational study in rats. Male rats were given cyclophosphamide (an anti-cancer drug, which is a known mutagen) prior to mating. The resulting offspring (F1 generation) were randomly mated, and the effects in the next generation (F2) assessed. This showed a significant increase in postimplantation loss, and in the F2 generation a significantly decreased mean foetal weight, and a significant increase in the number of malformed foetuses, with a range of malformations. They conclude that "exposure of the father to cyclophosphamide does result in a specific and heritable alteration in the fertility of the surviving 'apparently normal' F1 progeny. Interestingly, the adverse consequences of exposure of male rats to cyclophosphamide are similar in the F2 generation to those previously reported for the F1 progeny". This paper was published in 1992, and confirmatory studies would be valuable (Lindbohm, 1995), but none has been identified.

In an extensive review of 'animal models of human response to dioxins', which also reviews human studies (Grassman *et al.* 1998), the authors note that TCDD is the most potent member of the dioxin group, with the greatest affinity for the aryl hydrocarbon receptor (AhR). The estimated half life of TCDD is from 5.8 to 14.1 years, and the average adipose tissue concentration for U.S. residents is 5 ppt (parts per trillion). Human exposure is assessed by dioxin concentration in the lipid fraction of the blood, and typical levels are 36 to 58 ppt, with industrial exposures giving concentrations up to around 500.

Acute exposures with plasma levels exceeding 100 ppt may produce chloracne, and other disorders collectively referred to as 'Yu-Cheng'. In highly exposed chemical plant workers, plasma LH and FSH levels were positively correlated to lipid dioxins, and there was a trend to reduced testosterone. Children of Taiwanese women with Yu-Cheng showed disordered behaviour and impaired cognitive development at ages 6 to 7. A Dutch study suggested a reduction in psychomotor skills in breastfed infants related to an intake of contaminants, although there were also exposures to PCBs. Infants with high levels of dioxin in breast milk show elevated TSH (thyroid stimulating hormone) and lower T4 (thyroxin) levels, although

all were within normal clinical ranges. Decreased learning, reduced T4, and increased TSH, developmental delays, and immunological disturbances, have similarly been seen in exposed animals.

Industrial workers with dioxin levels of 25 to 500 ppt show increases in peripheral helper T-lymphocytes, and altered lymphocyte function in exposed subjects has been seen. Prenatal exposure in human infants produced changes in white cell populations at up to three months, and increased numbers of cytotoxic T-cells at 10 months. However immune function in children aged 6 to 10 years exposed in Seveso showed no abnormalities. In mice, dioxins suppress antibody responses and to a lesser extent T-lymphocyte responses.

This review (Grassman *et al.* 1998) notes that "most if not all of the biologic response elicited by dioxins are mediated by a cellular protein termed AhR to which TCDD binds specifically and with high affinity" (p. 766). Differences in affinity suggest that humans may be less sensitive than mice, and raise the possibility that as yet unidentified variant AhR alleles may influence susceptibility. However no relationship between a specific AhR genotype and response to dioxin has been demonstrated in humans.

Evidence from Seveso shows average serum levels in females approximately three times higher than in males 20 years after initial exposure. In rodents, TCDD appears to be a hepatic carcinogen in females but not in males, implying an interaction with oestrogens, and after Seveso there was an excess of liver cancer in women but not men.

Samet (1996) in an editorial on dioxin and cancer, emphasises the industrial exposures. It notes that "research findings on the mechanism of dioxin carcinogenesis have shown that risks in animals cannot be extrapolated directly to humans and that such extrapolations need to be mechanistically based".

Recent World Health Organisation risk assessment of dioxins and related chemicals

A consultation on the assessment of the health risks of dioxins, and a re-evaluation of the tolerable daily intake, was held in Geneva in May 1998 under World Health Organisation auspices. Draft reports from this include an executive summary (WHO, 1998), and working papers on human health effects after exposure to TCDD (Sweeney and Mocarelli, 1998), and health risks to infants from exposure to PCBs, PCDDs, and PCDFs (polychlorinated biphenyl, dibenzodioxin, dibenzofuran respectively) (Feeley and Brouwer, 1998). While this is useful as a very recent update on scientific work concerned with TCDDs and similar compounds, the focus is on health risks related to chronic relatively low dose intakes, although there is reference to the Seveso accident, food poisoning situations, and occupational exposures. While there is much useful information regarding health effects in exposed humans, and in exposed experimental animals, there is no new information on risks to children of exposed male subjects.

There are some results relevant to health effects in children of mothers exposed in pregnancy (WHO, 1998), page 11-12. Among children exposed *in utero* to background levels, effects include subtle developmental delays in U.S. children in the highest exposure categories and subtle thyroid hormone alterations in Dutch infants to age 3 months. The high exposure

groups in these studies had higher levels of PCBs as well as TCDD-like compounds. Children of mothers exposed in pregnancy to contaminated rice oil in Japan and Taiwan showed a range of skin defects, developmental delays, low birth weight, and other effects, but it was not clear to what extent dioxin-like compounds contributed to these effects, given the complexity of the exposures.

In regard to effects on exposed persons (Sweeney and Mocarelli, 1998), the section on reproductive hormones notes the previously-noted study of dioxin production workers showing changes in LH and FSH, and the negative findings from studies of Ranch Hand veterans. This review does not deal with effects in children.

In regard to health risks for infants after maternal exposure (Feeley and Brouwer, 1998), the report describes the rice contamination episodes which were observed in children born to mothers with estimated body burdens of 2-3 micrograms TCDD total toxic equivalent (TEQ) per kg body weight, confirmed by very high levels in placental samples. In other studies, a study of women who consumed moderate quantities of fish from Lake Michigan prior to and during pregnancy had infants who were of lower birth weight and smaller head circumference than infants born to women who did not eat Great Lakes fish. However in another study involving Lake Michigan sport fish consumers, it is stated that mean infant birth weight was positively associated with maternal fish consumption and PCB (polychlorinated biphenyl) exposure. A similar comparison in regard to Swedish mothers showed that those eating fish from Baltic Sea villages tended to have infants with lower mean birth weights and slightly smaller head circumference. Further follow-up of the Michigan cohort from 5 months to 11 years suggested some deficits in tests assessing memory, cognitive function and IQ. These differences were associated with cord blood PCB levels. There is a description of several studies relating primarily to developmental and psychological test assessments in conjunction with dietary exposures.

In the summary, it is noted that "except in the case of the two rice oil poisoning episodes, these effects are subtle and generally within normal population background variation". The psychomotor and cognitive function changes "can be classified as borderline effects". None of the studies reported relates to exposure of the father.

General comments on the likelihood of paternal exposures affecting children

The hypothesis that exposure of a male person to a chemical such as Agent Orange may be related to birth defects in offspring born later, or in health effects in such children occurring later in life, or in birth defects or other health effects in grandchildren, is difficult to assess. The great majority of studies of the teratogenicity or toxicity of a chemical are based on health outcomes relating to the individual who is exposed, or relating to births occurring after exposure of the mother during the relevant pregnancy or a relatively short time before. For example, nearly all the experimental data on the reproductive toxicity of pesticides is based on exposing pregnant female animals and observing effects in the offspring of that pregnancy. Most epidemiological studies deal with exposures of mothers, either close to the time of conception or in early pregnancy. The teratogenic effect of chemicals is usually attributed to

the direct chemical action on the developing foetus, rather than to an effect on the maternal genetic material.

In principle, a toxic exposure of a male could produce adverse health effects in subsequent offspring by several mechanisms (Wyrobek, 1994). The father could produce insufficient numbers of functional sperm, giving sub-fertility or sterility, for either genetic or environmental reasons. Damage to the father's germ cell DNA could affect subsequent conceptions, and damage such as a mutation could be passed on to live born surviving children, being present in their genetic DNA and therefore could be passed on to the next generation. Non-mutational changes to the father's DNA, 'epigenetic' changes, could affect foetal development. Sperm may carry 'prelesions', the impact of which will depend on the ability of the egg to repair the prelesion. The father's exposure to toxins could adversely affect a conceptus in ways other than by DNA, by being related to the small amount of cytoplasm present in sperm, or to other material in the ejaculate, or to some other means of transmission between the affected male and his partner.

An effect on genetic DNA, if present, would be most likely caused at the time of exposure of the male to the toxin or shortly afterwards, producing a permanent change in genetic material which would affect all conceptuses subsequently. On the non-DNA hypothesis, the effects would be related to the quantity of active toxin in the male fluids or sperm cytoplasm. This would be related to body levels of the toxin, and therefore any effect on a foetus would be expected to decrease with time after the initial exposure.

In regard to the question being addressed here, the only relevant studies are studies of exposures of males in relation to defects occurring in subsequently conceived offspring. There are no such studies with results suggesting a male reproductive hazard of dioxins in either humans or animals. Indeed, there is no clear or consistent evidence in humans of birth defects, childhood cancer, or other serious health outcomes in children or grandchildren conceived to males who have been exposed to any chemical toxin, or to ionising radiation (Olshan *et al.* 1994). Epidemiological studies have not shown detrimental effects such as increased birth defects among offspring of men who have received chemotherapy, and the extensive studies of survivors exposed to the atomic bomb explosions in Japan in 1945 have shown no genetic effects or increases in birth defects or cancer in the offspring (Buckley, 1994; Miller, 1994). A human epidemiological study (Little *et al.* 1996) shows no increase in leukaemia in the children of patients given the radioactive chemical Thorotrast, confirming previous negative studies for the children of radiation-exposed workers. However, there are studies in humans, which show increased chromosomally abnormal sperm in men who had received radiotherapy or chemotherapy for cancer (Wyrobek, 1994). There are a multitude of results showing associations between paternal occupation, or various paternal exposures, and birth defects, other reproductive outcomes, and childhood cancer in children of these men, but none of these are sufficiently consistent or strong to show a cause and effect relationship (Buckley, 1994; Savitz, 1994).

In mice or rats, there are studies which show the exposure of males to toxins before mating can produce developmental or behavioural abnormalities in offspring, and increases in cancer in offspring (Wyrobek, 1994). Increased malformations and decreased foetal weight in the second generation in experimental rats have been shown after treatment of male animals with cyclophosphamide (Hales *et al.* 1992). Recently results which suggest that in mice

preconceptional paternal exposure to plutonium-239 may render the offspring more susceptible to a second, chemical, carcinogen have been reported (Lord *et al.* 1998); these results need to be replicated and confirmed.

Summary

Dioxins are established carcinogens, producing a range of different types of cancer in animals and probably in humans. Human studies suggest excesses of a range of cancers in those directly exposed to high dosages of dioxins. Dioxins are also teratogenic in animals, and there is evidence of increased pregnancy losses, and some evidence of increased abnormalities in births to women with direct exposure.

There is however no evidence, either in humans or animals, that exposure of the male to dioxins can produce pregnancy problems or abnormalities in subsequently conceived offspring. There is evidence in animals that high doses of dioxin can produce testicular abnormalities and reduced sperm counts in males, which would be expected to be related to subsequent reductions in fertility. Such effects have not been seen consistently in humans, although there have been studies of these issues in Vietnam veterans and in civilian populations with high occupational exposures.

8. CHILDHOOD CANCER AND OTHER HEALTH CONDITIONS OCCURRING AFTER BIRTH.

Childhood cancer

The Veterans and Agent Orange Reports, 1996 and 1998 conclude that there is "inadequate or insufficient evidence", for any association with childhood cancer.

In regard to childhood cancer, the 1996 conclusion (Institute of Medicine, 1996) was that "two studies of Vietnam veterans found some suggestion of an increased risk of cancer among offspring. The evidence is, however, inadequate, given the lack of other studies failure to include chance and bias, and problems with herbicide exposure assessment" (p. 300). The 1998 report on this topic has not yet been seen, but the review group's conclusions are unchanged.

The results noted in the VAO 1996 report are primarily those of the CDC Vietnam Experience Study (Centers for Disease Control, 1988) which found an increase for childhood leukaemia (odds ratio = 1.6, confidence limits 0.6 - 4.0). Since then, the study from Seveso (Mastroiacovo *et al.* 1988) showed excess risks of all childhood cancer (relative risk 1.2), thyroid cancer (relative risk 4.6), Hodgkin's Disease (relative risk 2.0), and myeloid leukaemia (relative risk 2.7), although none of these was statistically significant, and the assessment of exposure was indirect, based only on area of residence.

Other conditions

The Veterans and Agent Orange Report, 1996 concludes that there is "inadequate or insufficient evidence", of any associations with other health conditions occurring after birth (Institute of Medicine, 1996).

Most of the studies reviewed are restricted to birth defects, that is, physical abnormalities present at birth or recognised soon after. The Vietnam experience study (Centers for Disease Control, 1989) (page 288-289) also assessed "physician-diagnosed major health problems or impairments during the first five years of their children's lives". About half of the reports were of respiratory disease, mostly asthma and pneumonia, and otitis media. Overall, more such health conditions were reported for Vietnam veterans than for non-Vietnam veterans (relative risk 1.3, limits 1.2 - 1.4), and after exclusion of birth defects or cancer as these are counted elsewhere, the overall risk ratio is 1.2 (limits 1.1 - 1.3). For specific conditions, elevated and significant risks were seen for anaemias, skin diseases, rash, and allergies. The VAO report comments that without validation from medical records, these excesses of generally minor common disease may well be due to recall bias.

Conclusions

Health conditions in veterans' children occurring after birth have apparently been assessed only in one study, and that was restricted to the first five years of life. Excesses of several common conditions were reported, but as this was based only on a questionnaire study without verification. The VAO document concludes that these excesses are likely to be related to recall bias.

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APPENDIX 1:

REVIEW OF MARCH 1998 PUBLICATION ON THE MORBIDITY OF AUSTRALIAN VIETNAM VETERANS (Commonwealth Department of Veterans' Affairs, 1998)

Limitations of this review.

It should be stressed that the document reviewed was a draft, pre-publication, copy of the executive summary of this report. These comments were sent to one of the authors of the report in December 1998, but no response has been received. It may be that further versions of the report may deal with many of the points raised in these comments.

The Australian survey

This reports a survey undertaken, presumably in 1966-97, of veterans identified in Australia. The survey was large, being based on 40,030 male veterans, representing an original roll of 59,036 from which those deceased or unmatched have been removed (Commonwealth Department of Veterans' Affairs, 1998). There are also smaller studies of 691 widowed, divorced or separated partners, and 223 female Vietnam veterans. The questionnaire used rather simple and general questions. The objective was to compare the results with expected results for Australian residents, but for many of the questions this was not possible, and even when a comparison was attempted, often the 'expected' numbers were based on very different methods of ascertainment and different questions. There has not been any attempt to validate the questionnaire information as yet, although this is recommended in regard to the major outcomes.

Strengths and weaknesses

The major problem with a study of this nature is the likely inaccuracy of responses. A questionnaire study using general questions as used here, applied to a group in which there is clear knowledge of potential exposures and there may be rewards and incentives attached to the reporting of certain conditions, would be expected on general grounds to give potentially severe bias in reporting, particularly towards the over-reporting of certain conditions.

For similar reasons, it would expected that there would be an incentive for those who had positive findings to report to participate, giving potentially severe selection bias.

These biases can be overcome, or ameliorated, in two ways. One is by the use of a simultaneous control group of subjects with similar incentives and disincentives to participate and report, and using identical methodology. An alternative to this is to assess within the surveyed group whether there are logically consistent results, for example an increase in the frequency of the reported condition amongst those with maximum levels of Vietnam service, or maximum exposures to particular agents such as Agent Orange. The other main protection

is to use the survey results only as an indicator for objective validation by review of medical records, direct assessment, or other methods. All three of these methods have been used in the U.S. Ranch Hand studies; none of them is used in this Australian report.

An alternative method which would be relatively free of bias could have been used for some conditions instead or as well as the questionnaire approach. This is to use linkage of identifying data on surviving and deceased veterans to data sources which would be reasonably complete for certain conditions, such as deaths by cause, cancers, and, at least in some Australian states, birth defects.

The main concession to these considerable methodological problems is that the conclusions include statements that the results for conditions showing large excesses should be "validated as a matter of urgency".

Response rate

The response rate to the survey of 49,944 male veterans was 80%. This is regarded as a good response. It is a relatively good response in terms of market research survey. It is not however a high response for a study assessing morbidity in a particular cohort. This is because it is almost certain that response would be influenced by health status. In epidemiological research of this nature, even a response rate of 90% is usually regarded as having considerable potential for non-response bias. In contrast to this study, the response rate in the Ranch Handers follow-up study was 99.9%, and the response rate in Pearce *et al.*'s study of New Zealand Operation Grapple veterans was 94% (Pearce *et al.* 1990). It is stated a telephone follow-up of non-respondents let the marketing research company conclude that "non-respondents did not pose a significant bias problem". The data on which this conclusion is based are not presented. The demonstration, for example, of similarity in age or socio-economic status which are often used as markers of non-response in market research surveys would not be sufficient to address the likelihood of response bias in a survey of this nature. Moreover the data given on the follow-up survey show that the response to that survey was quite low. Of 1,806 non-responders surveyed by telephone methods, contact was made with only 57%, and of those, only 35% responded. Selection bias cannot be dismissed. However the effect of it would be to reduce the prevalence of any reported condition by a maximum of 20%, which would apply if the outcome did not occur at all in the 20% of subjects who did not respond. As most of the differences reported are very large, this effect is relatively minor.

The response rate for questionnaires to partners was only 45%, and appropriate cautions are used in interpreting this data.

The fact that for many of the questions asked, comparable data for frequencies in the Australian population were not available, or could not be clearly interpreted, suggests that the questions were designed without consideration of the need to obtain data which could be compared to reliable sources.

Another methodological issue not discussed is that this survey is of morbidity in a survivorship group as, according to Figure 1, 15.6% of the original cohort of 59,520 Vietnam

veterans had died by the time this survey was carried out. This raises further questions about the comparability of this information to general population figures, as the population surveyed relates to one potentially dangerous exposure, but represents only living survivors many years after that exposure. The most likely potential consequence of this bias is that survivors might exclude those with the heaviest exposures and those who had had the greatest health problems, and therefore will tend to underestimate the total impact. There may be a selection for better health in those surveyed.

Results

Although for current purposes, the relevant parts of the report are only those on the health of children, the general results are relevant.

The results for the veterans themselves show in general much higher frequencies of reported health problems than are estimated from general population data. In many situations however the question asked of the veterans was wider and less specific than that used in the comparison data. The potential of variations in questions to produce great differences in results is shown by the data on migraine, where there is an almost ten fold difference in the various expected numbers given, depending on different survey questions used. For insomnia and sleep disturbance, the differences in the estimated expected numbers are 32 times. Large differences are seen even for physical conditions such as cirrhosis of the liver, where the expected estimates show a range of 30 times. In general most conditions show excesses of reported versus expected figures, with the striking exception of impotence, where the number of cases reported is less than half of the expected figure.

Particularly high ratios of reported as compared to expected results are seen for haemorrhoids (5 times) and post traumatic stress disorder (4 times). Excesses are seen for most cancers, with the difficulties in interpreting the questions being highlighted. Particularly large excesses are seen for soft tissue sarcoma (15 times), cancer of the colon (3.5 times), male breast cancer (17 times), and eye cancer (9 times). Cancer of the prostate is reported three times more frequently than expected, whereas non-cancerous disease of the prostate is reported only one third as frequently as expected. Motor neurone disease was reported by 1298 veterans, compared to an expected number of two, but this latter number is based on a detailed survey; it is noted that the mortality study of these veterans showed a similar number of deaths from this cause compared to the number of deaths expected. This comment also applies to some other morbidity situations.

These brief comments are sufficient to show that it is not possible to interpret the results of this survey in terms of comparisons to general population results. This is because the questions are too limited and non-specific to allow appropriate comparisons, the potential of unconscious or conscious variation in response to questions is potentially high and cannot be assessed, and it is likely that those with health problems were more likely to respond to the survey. In most instances where large differences are seen, and relevant other studies are available, similar differences in mortality have not been observed, and increases of similar magnitude have in general not been seen in comparable studies done in other countries of Vietnam veterans or groups exposed to dioxins.

Results in regard to health of children

Twenty-one percent of respondents said that they and a partner had tried for more than 12 months to conceive without success. This is 1.5 times the expected number which is quoted, although the response to this type of question would be expected to vary greatly with the method of questioning used. The number of veterans who say they have ever fathered any children was 87% and almost identical to the expected number.

The report is confusing in regard to the denominators used in the comparison of birth outcomes. The question D4 on how many children they have fathered (from 1966-1977) gave an aggregate response of 70,867. In D5, veterans were asked to give the year of birth and gender for each of the children. It is then stated that the greatest number of children born were between 1973 and 1978, a total of 29,789. It is not clear how these questions were used to interpret the later results. It is stated (page 59) that data from question D4 were used as the denominator for questions D7 and D8, whereas data from question D5 were used as the denominator for question D11. Yet, questions D7 and D8 themselves in their wording refer to the list given in D5, whereas question D11 relates to all children born at any time. Moreover, question D5 simply asks for a list of all the children who are noted in question D4, so should give the same total.

A further problem is that question D4 relates to children *conceived*, and if carefully answered, would include the 12,773 stillbirths, miscarriages and terminations reported in question D2. The expected numbers of deaths, cancers and birth defects are calculated from sources which are based only on *live births*, introducing another problem into the comparison.

Conditions assessed

"Sight problems not able to be corrected by spectacles" (question D6.1). There were 2376 instances reported, and a figure of 8% is given, which is this figure divided by the number of children born in 1973-1978, given under question D5. This implies that question D5 in fact asked the year of birth and sex only of children born between 1973 and 1978. This aspect of the methodology needs to be clarified. The expected number was 50% *reduced* compared to the expected number quoted.

"Long term hearing problem or ear problem" (question D6.2). The number reported was only 13% of the expected number. Again the percentage shown suggests that the number reported was compared to the 1973-78 children born. The expected number in this case comes to 79% of the *total* number of children, which is inconceivable. It seems clear that the interpretation of these data in terms of the appropriate denominator, and the calculation of the expected number, even with the limitations given, are likely to be grossly in error.

Questions D7 and D8 apply to specific major abnormalities, and the percentages given suggest that the numbers have been related to the total number of children born in 1973-78,

although the text says that the numbers should be related to the total number of children born at any time. It is similarly not clear how the expected numbers are generated. As reported, there is a large excess of all abnormalities given, ranging from a 50% excess of Down's Syndrome to a 10 times excess of spina bifida and of absent body parts, and a 4.5 times excess of other abnormalities. However with all the difficulties given, these data do not permit any interpretation. There is some discussion of the fact that not all abnormalities are present at birth, and for some there has been a secular decline in time, but these are relatively minor problems compared to the issues of accuracy in reporting, and the calculation issues in the report itself.

Question D9 on cancers in children is also similarly complicated. The question specifically relates to D5, although it is stated on page 59 that D5 was used as the denominator only for D11. It is stated that 730 cancers were reported, being 103 per 10,000 children, which is a prevalence rate based on the total given in D4. The excess for all cancers is about twice normal, with six times the expected number of Wilms' tumour, twice the number of tumours of the nervous system, and a 30% increase for leukaemia.

Question D10 relates to any other major illness in the children listed under D5. The results are referred to Appendix C1, which was not included with the summary available to this reviewer.

Question D11 asks about deaths in all children born at any time, divided into three categories, illness, suicide, and accident/other. Childhood cancer makes up a substantial proportion of childhood deaths from illness. Comparison of questions D11 and D9 shows that the expected numbers of total cancers as a proportion of expected deaths from illness is 0.41. For the reported numbers, the total cancers reported is almost equal to the total deaths from illness (ratio 0.87) which is consistent with severe over-reporting of cancers in comparison to deaths from illness. The data show similar numbers as expected for illness, three times the expected number for suicide, and twice the expected number for accidents. Total deaths are not calculated. The total by addition is 1,908, 2.7% of the total children reported, compared to an expected of 1,245, an increase of 50%.

Summary

This report is seriously flawed in many ways and can be interpreted only in terms of indicating impressions and perhaps beliefs on the part of Vietnam veterans. The great excesses reported in many conditions, both in veterans and in their children, the form of the questions used, and the potential bias from non-response, all suggest that the data reported on numbers of health events is likely to be an extremely poor indicator of the real frequency of occurrence, and in many instances, it may be a considerable overestimate. In most instances, the questions have not been designed in a way that the data reported are comparable to the available sources of expected numbers.

This report does not add usefully to existing evidence from more reliable sources on likely health effects in Vietnam veterans and their children. No clear interpretation is possible on the basis of such a potentially flawed study. The methodological problems are so severe that

the report is likely to be seriously misleading. The results should be used until the methodological issues have been addressed. Validation of reported results is necessary.

There are reasonable grounds for concluding that the general problems are in the direction of over-reporting. If this is accepted, the data collected could be used to guide a validation study, in which follow-up studies are carried out only in regard to specific conditions as reported by respondents. This however does assume that all the bias is in the direction of over-reporting, and that further validation would not lead to the documentation of health situations in those who have not responded to the questionnaire, or those who have responded negatively to those particular questions.

A much superior method of obtaining reliable information would be to use record linkage techniques rather than an interview approach. It should be possible, for example, to link data on individuals who have served in Vietnam to mortality data (as has indeed been done). It should also be possible to link such data to cancer incidence data in the whole of Australia, and in some states to birth records and congenital abnormality records. This may not be possible for the whole country, and such sub-studies might only be possible for veterans who live in certain states where there are good data systems. However accurate information for such sub-groups would be more valuable than potentially seriously biased information for the entire group.

Implications for New Zealand

The results of this study are not helpful in addressing the potential health issues in New Zealand. The potential biases and problems in the study are so severe that the results are likely to be seriously misleading, and they should not be used until further studies involving objective validation are carried out.

This experience demonstrates the problems in using questionnaire approaches, particularly with brief and non-specific questions, the difficulties in estimating expected frequencies of health outcomes, and the greater value in using methods reliant on objective data and studying the entire group of veterans.