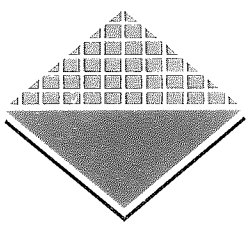
Dapsone exposure, Vietnam service and cancer incidence

A report to the Scientific Advisory Committee to the Minister for Veterans' Affairs



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The Hon. Ben Humphreys,
Minister for Veterans' Affairs,
Parliament House,
CANBERRA, ACT 2600.

Dear Minister,

I have pleasure in submitting the report of the study, *Dapsone Exposure, Vietnam Service and Cancer Incidence*. This study was carried out by the Australian Institute of Health and Welfare with review from the Scientific Advisory Committee.

Yours sincerely,

Professor G. Berry
Chairperson of Scientific Advisory Committee
for the Study of Carcinogenicity of Dapsone

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The Hon B. C. Humphreys MP
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295 Ann Street
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Dear Minister

I am pleased to transmit herewith the final report of the investigation of the carcinogenicity of Dapsone in Vietnam veterans which was conducted by this Institute.

Yours sincerely

L R Smith

Dr L R Smith
Director
21 December 1992

Executive summary

Background

Perceived ill-health of Vietnam veterans and their families has been a public issue since 1978. Initially, the major concern was possible effects of exposure of Vietnam veterans to some herbicides (notably Agent Orange) used during the Vietnam conflict.

Two studies, of mortality among Vietnam veterans and of birth defects in their children, were commissioned by the Commonwealth Government in the early 1980s but did not find any effects attributable to the use of chemicals in Vietnam. The Royal Commission into the Use and Effects of Chemical Agents on Australian Personnel in Vietnam was established in 1983.

Dapsone was one of the chemicals reviewed by the Royal Commission. During the Vietnam conflict Australian forces had used this drug, initially for the treatment of falciparum malaria and later also for its prevention. The Royal Commission recommended studies into the carcinogenicity of dapsone. The recommendation was supported by the Hogg report, which was commissioned by the Commonwealth to coordinate its response to the findings of the Royal Commission.

The Department of Veterans' Affairs asked the Australian Institute of Health and Welfare (AIHW—then called the Australian Institute of Health) to conduct a study of cancer incidence in relation to dapsone use. A protocol, completed in November 1990, defined the study aims and design, dealing with data collection and analysis, limitations of the study, reporting, and privacy. This protocol was accepted by the Scientific Advisory Committee formed to advise the Minister for Veterans' Affairs on the study, the State and Territory cancer registries, and the AIHW Ethics Committee.

Dapsone

Dapsone (4,4'-diaminodiphenyl-sulphone) is a sulphonamide-like drug that probably acts by inhibiting folate synthesis. Folate synthesis is an essential metabolic step in those unicellular organisms that, unlike humans, cannot use preformed folates. Dapsone is used for short- and long-term treatment of leprosy and for the prevention and treatment of malaria. Adverse reactions to its use include haemolytic anaemia, methaemoglobinaemia, peripheral neuropathy, gastrointestinal symptoms, fever, pruritus and various rashes.

Despite dapsone's widespread clinical use for many years, there is little evidence that it is associated with an increased risk of cancer. There are case reports of cancers among persons who have taken dapsone, but no specific or unusual site of cancer consistently appears in these reports. None of the reports gives a biological argument for an association of specific cancers with dapsone use. Moreover, most of the patients described in these reports had leprosy and had taken dapsone at higher doses and for much longer than was the case with dapsone used prophylactically against or as treatment for malaria by Australian servicemen.

Chronic carcinogenicity studies undertaken in both rats and mice show limited evidence of carcinogenicity. Mutagenicity studies have also been equivocal.

In the absence of further data, the International Agency for Research on Cancer has been unable to determine whether dapsone should be regarded as a carcinogen of humans.

Sites of cancer of a priori interest

For dapsone exposure, the sites of cancer that have been noted in previous studies are non-Hodgkin's lymphoma, Hodgkin's disease, oral cancer, kidney cancer, bladder cancer and leukemia. Because of the earlier interest in herbicides, this study also examines cancer incidence for sites of cancer that have been hypothesised as being related to herbicide exposure: non-Hodgkin's lymphoma, Hodgkin's disease, soft tissue and other sarcoma, nasal cancer, nasopharyngeal cancer, thyroid cancer, testis cancer and primary liver cancer.

Design of this study

The aim of this study was to assess and quantify any association between cancer incidence and exposure to dapsone and to Vietnam service among Australian Army servicemen who served in Vietnam during the Vietnam conflict.

The study cohort ('servicemen') consisted of all 115,407 males who served in the Australian Army for at least one year between 1 January 1965 and 1 March 1972. Identification of servicemen, those who had been exposed to dapsone, and those treated for malaria was done through Army records. Cancer incidence was determined by reference to State and Territory cancer registry records for the period 1972 to 1989, although not all registries had complete coverage for all of this period. Cancer incidence was examined for all cancers, and for 28 sites of cancer that included the cancers of a priori interest as well as groupings with more than 30 incident cases.

Cancer incidence rates, controlling for age and calendar year, were compared for several subgroups of servicemen:

- dapsone-exposed Vietnam veterans compared with non-exposed Vietnam veterans;
- for dapsone-exposed Vietnam veterans, those with the higher exposures compared with those with the lower exposures;
- Vietnam veterans with malaria compared with other Vietnam veterans;
- Vietnam veterans compared with non-veterans;
- dapsone-exposed Vietnam veterans compared with non-veterans;
- servicemen compared with other males in the Australian population.

Where possible, these comparisons were made separately for National Service (conscript) and Australian Regular Army (volunteer) servicemen.

Cancer mortality was not directly assessed.

Cancer incidence and dapsone exposure

Total cancer incidence

A total of 509 cancers were identified among Vietnam veterans. The relative cancer incidence rate at all sites combined for dapsone-exposed servicemen compared with other Vietnam veterans was 0.88. The 95 per cent confidence interval (95% CI) for the relative rate is 0.74 to 1.05, which includes equal incidence rates in both groups. The upper limit shows that the data from this study are inconsistent with a markedly higher total cancer incidence among dapsone-exposed servicemen compared with other Vietnam veterans; that is, there is no evidence from this study of an excess of overall cancer occurrence in those Vietnam veterans who had taken dapsone.

Relative cancer incidence rates among dapsone-exposed Vietnam veterans compared with other Vietnam veterans: all sites

Number of cancer cases among Vietnam veterans			
Exposed to dapsone	Not exposed to dapsone	Relative incidence rate	95% CI
247	262	0.88	(0.74, 1.05)

Most servicemen who took dapsone took a total (cumulative) dose of less than 5 grams. Dapsone-exposed servicemen whose total dose of dapsone differed by 5 grams were estimated to have a 1.1-fold difference in their overall cancer incidence rate. The 95 per cent confidence interval, 0.8 to 1.5, is consistent with no difference in cancer incidence for servicemen exposed to different doses of dapsone. The upper limit of this confidence interval shows that the data from the study are inconsistent with large differences in total cancer incidence for servicemen exposed to different total doses of dapsone; that is, Vietnam veterans who took more dapsone did not appear to be much more likely to develop cancer than those who took less dapsone.

Different sites of cancer

For none of the 28 sites of cancer examined was the cancer incidence among the dapsone-exposed servicemen statistically significantly greater than that among other Vietnam veterans. For no site of cancer examined was there a statistically significant dose–response relationship between the total amount of dapsone received and cancer incidence.

For one cancer, that of the testis, the rate of occurrence was much less than expected. On biological and statistical grounds, this apparent protective effect of dapsone probably reflects chance alone.

Specific sites of cancer

Six sites of cancer—non-Hodgkin's lymphoma, kidney, Hodgkin's disease, bladder, oral and leukemia—were of particular interest because previous research,

independent of this study, had suggested that they might be associated with dapsone exposure. None of these sites had, however, shown particularly marked relationships with dapsone exposure in these other data sets. This was also the case in this study.

Relative cancer incidence rates among dapsone-exposed Vietnam veterans compared with other Vietnam veterans: specific sites

Cancer site	Number of cancer cases among Vietnam veterans: Exposed to dapsone	Not exposed to dapsone	Relative incidence rate	95% C
Non-Hodgkin's lymphoma (ICD 200, 202)	19	9	1.8	(0.8, 3.9)
Kidney (ICD 189)	6	6	1.3	(0.4, 4.1)
Hodgkin's disease (ICD 201)	7	4	1.2	(0.3, 5.5)
Bladder (ICD 188)	13	14	1.0	(0.5, 2.1)
Oral (ICD 140–146, 149)	16	27	0.6	(0.3, 1.1)
Leukemia (ICD 204–208)	7	13	0.5	(0.2, 1.2)

Dose response among dapsone-exposed Vietnam veterans: specific sites

Cancer site	Relative incidence rate for doses differing by 5 grams	95% CI
Non-Hodgkin's lymphoma (ICD 200, 202)	0.5	(0.2, 1.4)
Kidney (ICD 189)	0.5	(0.1, 3.1)
Hodgkin's disease (ICD 201)	1.2	(0.2, 6.6)
Bladder (ICD 188)	2.1	(0.6, 7.3)
Oral (ICD 140–146, 149)	0.9	(0.3, 2.7)
Leukemia (ICD 204–208)	1.8	(0.3, 9.9)

For none of these six sites was the cancer incidence particularly high among dapsone-exposed servicemen compared with other Vietnam veterans. None of the relative incidence rates was statistically significantly different from equal cancer incidence rates in the two groups of servicemen. The dose–response relationships were also unremarkable.

The observed relative rates are similar to those for total cancer incidence and for other sites of cancer. If dapsone exposure were causing some cancers, increased cancer incidence should be apparent among some or all of these six specific sites of cancer, even if the elevation in rates was not statistically significant. Cancer incidence

for these six sites, individually and collectively, cannot be taken as definite evidence that dapsone exposure has led to an increased number of cancers.

The wide confidence intervals for some comparisons show, however, that this study has low power to detect differences in cancer incidence for some sites of cancer. The maximum latency period between dapsone exposure and registration of a cancer is 24 years, so an increase in cancer incidence 20 or more years after exposure to dapsone may not be detected by this study.

Cancer incidence and Vietnam service

Total cancer incidence

The study identified a total of 1,638 cancers among the servicemen. The overall relative cancer incidence rate for Vietnam veterans compared with non-veterans (those servicemen who had not been posted to Vietnam) was 0.99. The 95 per cent confidence interval for the relative rate is 0.89 to 1.10, which includes equal incidence rates in both groups. The upper limit shows that the data from this study are inconsistent with a markedly higher total cancer incidence among Vietnam veterans compared with non-veterans.

Relative cancer incidence rates among Vietnam veterans compared with non-veterans: all sites

Number of cancer cases among servicemen			
Served in Vietnam	Did not serve in Vietnam	Relative incidence rate	95% CI
509	1,129	0.99	(0.89, 1.10)

Different sites of cancer

For none of the 28 sites of cancer examined was the cancer incidence among Vietnam veterans statistically significantly greater than that among non-veterans. This was also true for servicemen who had served as volunteers in the Australian Regular Army. Among National Servicemen three sites of cancer—pancreas, lung and brain—showed statistically significantly higher incidence among Vietnam veterans compared with non-veterans.

Relative cancer incidence rates among Vietnam veterans compared with non-veterans: selected sites

	National Service				Australian Regular Army			
	No. of cases		Relative incidence		No. of cases		Relative incidence	
Cancer site	VV	NV	rate	95% CI	VV	NV	rate	95% CI
Pancreas (ICD 157)	7	1	11.0	(1.4, >10)	6	24	0.9	(0.4, 2.1)
Lung (ICD 162)	13	6	3.9	(1.5, 10.0)	46	158	0.8	(0.5, 1.1)
Brain (ICD 191)	8	7	3.0	(1.1, 8.2)	9	14	1.0	(0.4, 2.3)

Note: 'VV' denotes Vietnam veteran; 'NV' denotes non-veteran.

There was nothing in the medical literature to link these three sites of cancer with Vietnam service. Curiously, any increased risk is apparently confined to National Servicemen because the estimated risks for these sites of cancer among members of the Australian Regular Army are not greater than unity. This could, however, occur if there were some relevant aspect of Vietnam service that differed substantially between these two groups of servicemen.

One statistical consideration is that these three nominally statistically significant results have occurred when testing for differences at 29 sites in the two service groups. With so many tests, it is to be expected that, even if there were no real underlying difference, chance would result in a few being nominally statistically significant. For 58 tests, the expected number of nominally statistically significant raised estimates is 1.4, and observing three such results is not unusual.

Specific sites of cancer

Eight sites of cancer—nasopharyngeal, primary liver, non-Hodgkin's lymphoma, Hodgkin's disease, soft tissue, thyroid, testis and nasal—were of particular interest because previous research, independent of this study, had nominated them as possibly being associated with herbicide exposure. The following table shows relative cancer incidence rates for these sites.

Relative cancer incidence rates among Vietnam veterans compared with non-veterans: specific sites

Cancer site	Number of cases: Vietnam veterans	Number of cases: Non-veterans	Relative incidence rate	95% CI
Nasopharyngeal (ICD 147)	4	1	5.8	(0.6, >10)
Primary liver (ICD 155)	3	2	3.0	(0.3, >10)
Non-Hodgkin's lymphoma (ICD 200, 202)	28	47	1.1	(0.7, 1.8)
Hodgkin's disease (ICD 201)	11	22	1.1	(0.5, 2.2)
Soft tissue and other sarcoma (ICD 170–171)	10	19	1.0	(0.4, 2.1)
Thyroid (ICD 193)	3	8	0.9	(0.1, 3.5)
Testis (ICD 186)	26	57	0.8	(0.5, 1.2)
Nasal (ICD 160)	1	3	0.4	(0.0, 5.3)

If herbicide exposure were causing some cancers and if Vietnam veterans were exposed to herbicides, increased cancer incidence should be apparent among some or all of the specific sites of cancer, even if the elevation in rates was not statistically significant. For no site is cancer incidence among Vietnam veterans statistically significantly different from that among non-veterans. The two highest and the lowest estimated relative rates are based on five or fewer cancer cases, and the confidence intervals are correspondingly wide. The other five estimated rates, based on more than 10 cancer cases, are close to unity. Cancer incidence for these five sites of cancer, individually and collectively, cannot be taken as definite evidence that posting to Vietnam has led to an increased number of cancers.

Conclusion

The study revealed no definite evidence that dapsone exposure was associated with an increase in total cancer incidence. Cancer incidence was assessed at six sites that had been suggested in previous publications as those for which an effect of dapsone was most likely. The study does not provide definite evidence of increased cancer incidence at these sites. Similar conclusions apply to the other 22 sites that were examined.

The study revealed no definite evidence that Vietnam service was associated with an increase in total cancer incidence. Cancer incidence was assessed at eight sites that had been suggested in previous publications as those for which an effect of exposure to herbicides was most likely. The study does not provide definite evidence of increased cancer incidence at these sites. Similar conclusions apply to the other 20 sites that were examined.

For those sites of cancer with few cases the confidence intervals were wide. The study results cannot therefore rule out an increased incidence at one or more of these sites.

The most recent cancer registration used in this study was for 1989, 24 years after first exposure to dapsone or service in Vietnam. Accordingly, this study cannot detect cancers that may arise at greater latencies after exposure to dapsone or Vietnam service.