THE HEALTH IMPACT OF PESTICIDE EXPOSURE IN A COHORT OF OUTDOOR WORKERS

BY

JOHN BEARD

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ABSTRACT

This thesis describes a study undertaken between 1992 and 2001 to explore the possible health impacts of human exposure to pesticides. The study followed the health outcomes of approximately 4000 outdoor workers over a period of up to sixty-one years. These workers comprised two subcohorts of approximately even size, one composed of agricultural workers with high insecticide exposures, and the other made up of outdoor staff from local councils in the same area with little or no occupational exposure to insecticides. Mortality and morbidity were compared between the two groups, and with the general Australian community.

The study identifies significantly increased mortality among both exposed and control subjects when compared to the Australian population. The major cause of this increase was mortality from smoking related diseases. The study also identifies significant increases in mortality among exposed subjects for a number of conditions that do not appear to be the result of smoking patterns, both when compared to the control group and the Australian population. These include pancreatic cancer in some DDT exposed subjects and asthma, diabetes, and leukaemia in subjects working with more modern chemicals. There was also an increase in self reported chronic illness and asthma, and lower neuropsychological functioning scores among surviving exposed subjects when compared to controls. Diabetes was also reported more commonly by subjects reporting occupational use of herbicides.

DECLARATION

I hereby declare that the material contained in this thesis has not been published elsewhere, except where due reference is made, and that this thesis has not been used to obtain any other academic award.

John Beard

December 2001

To Christine for her love, support and understanding.

To Jessie, Malcolm and Jordan for their inspiration.

PREFACE

This Doctor of Philosophy (PhD) thesis describes the methods and findings of an historical cohort study undertaken on the north coast of New South Wales (NSW) to examine the health impact of high pesticide exposures among staff of the NSW Board of Tick Control. The *North Coast Outdoor Workers Study,* as it came to be known, was prompted by widespread community and worker concern that these exposures might be resulting in a number of adverse outcomes. The study was undertaken by the Northern Rivers (formerly North Coast) Public Health Unit in response to these concerns and as part of its involvement in the NSW Cattle Tick Dip Management Advisory Committee.

As the principle investigator for this study I had sole responsibility for

- Its conception, planning and management;
- Reviewing the related literature;
- Developing the study design and analysis strategy;
- Overseeing the collection, entry and cleaning of data;
- Data analysis (in conjunction with co-investigators as outlined below);
- Interpreting results;
- Writing associated reports and papers now in preparation.

The role of my co-investigators in this study was as follows:

- Mr. Tim Sladden developed SAS programs for calculation of SMRs and SIRs based on programs given to us by Dr. Stephen Corbett;
- Dr. Geoff Morgan provided extensive assistance in further refining these programs;
- Dr. Lyndon Brooks undertook some of the analysis relating to the survey of surviving cohort members.

A number of research assistants also participated in the study. Their roles were:

- Ms. Jan Atkins searched records and undertook extensive interviews to identify members of the exposed cohort. Jan also entered much of the original data on these subjects;
- Mr. Mark Dowling further developed the database and oversaw the follow-up of non responders to the questionnaire survey;
- Ms. Margaret Leedow cleaned the dataset and undertook further data entry;
- A number of other research assistants telephoned non responders to the questionnaire and encouraged their participation;
- Ms. Ria Maximilian created the questionnaire database and entered the questionnaire data.

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I wish to particularly thank Mr. Tim Sladden and Dr. Geoffrey Morgan for their remarkable patience while developing the analytical programs. I am also grateful to Dr. Stephen Corbett for providing me with SAS programs that formed the basis for much of this analysis.

I am also grateful for the assistance of:

- NSW Agriculture for providing access to their records and staff;
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- Ms. Jan Atkins for her initial work with the Dippers themselves;
- Mr. Mark Dowling for overseeing subject follow-up and with the database;
- Ms. Margaret Leedow for help with the databases;
- Ms. Ria Maximillien for her work on the survey database;
- Dr. Paul Jelfs at the Australian Institute of Health and Welfare for his support matching the cohort with the National Deaths Index;
- Ms. Diane Loza for assistance with presentation;
- Mr. John Simpson, Mr. Geoff Sullivan and Mr. Joe Holloway for assistance in gathering information on local work practices;
- The Northern Rivers Area Health Service for funding the study;
- The NSW Public Service Association for assistance contacting subjects;
- Participants in the study for their good humoured but conscientious contributions.

I would also like to thank all the members of my team at the Southern Cross Institute of Health Research and the Population Health Directorate of the Northern Rivers Area Health Service for their tolerance and understanding.

ACRONYMS

ANOVA	**Analysis of Variance**
BMJ	**British Medical Journal**
CI	**Confidence Interval**
DDE	**DDT metabolite p,p'-dichlorodiphenyldichloroethylene**
DDT	**1,1,1-trichloro-2,2'*bis*(*p*- chlorophenyl) ethane**
HIC	**Health Insurance Commission**
ICD	**International Classification of Diseases**
IHD	**Ischaemic Heart Disease**
LCL	**Lower Confidence Level**
LGA	**Local Government Area**
OR	**Odds ratio**
PMR	**Proportional Mortality Ratio**
ppb	**Parts per Billion**
ppm	**Parts per million**
SIR	**Standardised Incidence Ratio**
SMR	**Standardised Mortality Ratio**
UCL	**Upper Confidence Level**

DEFINITIONS

Pesticide
Pesticides have been defined as "any substance or mixture of substances intended for preventing, destroying, repelling, or mitigating any pest"(Klaassen 2001). The term pest includes harmful, destructive, or troublesome animals, plants or microorganisms.

When discussing possible exposure to these chemicals, this study has used the generic term "pesticides" except when referring to a specific subset of chemical.

Insecticide
Pesticides used in the control of insects.

Herbicide
Pesticides used in the control of plants.

A Dipper prepares to treat cattle

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1 INTRODUCTION

Inorganic chemicals have been used to control pests since classical Greece (Smith and Secoy 1975). However, it was only during and after the Second World War that the intensive development and use of synthetic chemicals first occurred. The discovery in 1939 that 1,1,1-trichloro-2,2'*bis*(*p*- chlorophenyl) ethane (DDT) was an effective pesticide heralded a new era in agriculture and insect control. Other insecticides quickly followed including organophosphates, carbamates, synthetic pyrethroids and other organochlorines. The use of DDT, in particular, became so widespread that within 30 years it could be detected in Antarctic ice cores, even though it had never been used on that continent (WHO 1979).

These chemicals revolutionised agricultural practice and are thought to be largely responsible for malaria eradication in the United States and Italy (Attaran and Maharaj 2000). Initial studies of their possible health effects on humans were small and reassuring (Hayes and Durham 1956). By the 1960's, however, the widespread use of DDT was having noticeable impacts on ecological communities, and researchers began to undertake more comprehensive epidemiological investigations into the impact of pesticides on humans. These studies faced numerous limitations common to environmental epidemiology, and the literature review that follows suggests that, even today, our understanding of the relationship between pesticides and human health is poor.

This thesis describes a study undertaken between 1992 and 2001 to explore the possible health impacts of pesticide exposure. The study followed the health outcomes of approximately 4000 outdoor workers over a period of up to sixty-one years. These workers comprised two subcohorts of approximately even size, one composed of agricultural workers with high insecticide exposures, and the other made up of staff from local councils in the same area with little or no occupational exposure to insecticides. Mortality and morbidity were compared between the two groups, and with the general Australian community.

1.1 BACKGROUND TO THE STUDY

The main group investigated in this study comprised all identifiable field staff of the New South Wales Board of Tick Control employed between 1935 and 1995. This agency was established in 1920 to control the spread of the cattle tick into New South Wales (NSW) from neighbouring Queensland. Cattle ticks were introduced into the north of Australia in 1872 and gradually extended their range south (Williams 1995). They are the carrier of blood borne protozoan parasites that may cause large outbreaks of serious illness and death in susceptible cattle (Figure 1-1).

Figure 1-1 (from Williams) Animal carrying a heavy burden of cattle tick

Because of the threat the insect posed to the local cattle industry, the NSW Government established a cattle quarantine area and tick control program in northeastern NSW and along the Queensland border. The scale of this program was large, with over 1600 cattle dips constructed in this area, the vast majority of which were run by staff from the NSW Board of Tick Control (Figure 1-2). Over three thousand staff worked on the program after its inception. All cattle entering the quarantine area were required to be run through dips, and all cattle raised in the area were also required to be regularly dipped.

Figure 1-2 (after Williams) Location of Dip sites in the Tweed Valley of Northern NSW

From 1920 to 1955, the tick control program focused on controlling and quarantining potentially affected cattle. The only chemical available for this purpose was arsenic, which was moderately effective, unpleasant to work with, and its benefits were short-lived. With the advent of DDT, however, hopes were raised that it might be possible to totally eradicate the cattle tick from the entire area. During the late 1950's, a large number of new staff were employed and a rolling program of eradication undertaken. By the early 1960's, most of the area's 1700 dips contained DDT. By 1962, however, it became apparent that tick resistance to this chemical was developing, and the first of a new range of chemicals including pyrethroids, organophosphates and carbamates were introduced into the program. These have continued to be the mainstay of treatment to the present time.

The effectiveness of this program in controlling tick outbreaks can be seen in the reduction of tick infested properties from an average of 700 per year during the 1950's to 10 per year during the 1990's (Williams 1995). This has allowed both the size of the Tick Quarantine Area and the number of staff involved with the dipping program to be dramatically reduced over the same time period. While in its heyday, the program employed many hundreds of staff at any one time, today only a few full time staff remain, and most of the responsibility for tick control has been passed on to property owners.

The daily work of field staff employed on the tick control program included maintaining the concentration of chemicals within the dips, treating the cattle, and cleaning the resulting hair and scum from the bath. Reports from members of the cohort who were interviewed during this study indicate that, in the course of this work, staff faced extremely high and recurrent exposures to the insecticides being used (Figure 1-3).

In the late 1980's, the union representing dip staff raised concerns that these exposures might have been the cause of higher than expected rates of cancer in staff who had worked on the tick control program. These concerns were highlighted in a television documentary aired nationally in 1989.

Figure 1-3 Cattle being dipped

In the early 1990's, community concern was also raised when it became apparent that a number of old dips had been dismantled and the sites used for residential development. Since past practice had been to dispose of the chemicals used in dips in a shallow hole on site, and since many of the chemicals used are extremely persistent in the environment, concerns were raised that the health of residents may be affected by residual soil contamination. In response to these concerns, the NSW Government convened the Cattle Tick Dip Site Management Advisory Committee (DIPMAC). DIPMAC identified a total of 41 houses that were thought to have been built on or immediately adjacent to former dip sites. The level of this contamination (up to 100,000 mg DDT/kg soils and 3,000 mg arsenic/kg soils) was well above the recommended health investigation thresholds (Beard, Williams et al. 1992).

DIPMAC therefore commenced a process of health risk assessment for these residents. To help inform this assessment, and to examine the impact of past occupational exposures to these chemicals, DIPMAC, through the NSW Health Department, initiated the study of the health of past and present staff of the NSW Board of Tick Control that forms the basis for this thesis. Because of their high exposures, and because the extended follow-up period for many staff allows time for disease development, "Tick Dippers" provide an ideal group in which to investigate whether exposure to these substances might be related to adverse health outcomes in the longer term.

1.2 AIM OF THE STUDY

The aim of this study is to determine whether the occupational exposure to insecticides of current and past field staff of the Board of Tick Control adversely influenced their health.

1.3 HYPOTHESIS TO BE TESTED

That repeated high exposure to insecticides in an historical cohort of agricultural workers increased their rates of death and morbidity compared to a control cohort and the Australian population.

2 EPIDEMIOLOGICAL STUDIES OF INSECTICIDE EXPOSURE

2.1 HISTORICAL PERSPECTIVE

The first recorded use of inorganic chemicals to control insect pests comes from classical Greece where Homer mentioned the value of burning sulphur as a fumigant (Smith and Secoy 1975; WHO/UNEP 1990). In Roman times, Pliny the Elder recommended the use of arsenic as an insecticide, as well as a mixture of soda and olive oil to treat legume seeds. In the sixteenth century, the Chinese appear to have independently discovered the value of arsenicals and soon afterwards tobacco extracts were used in Europe.

The mid nineteenth century saw a systematic scientific approach applied to the development of possible pesticides. Pyrethrum, a natural insecticide derived from chrysanthemum flowers, and soap were widely used, as was a combined wash of tobacco, sulphur and lime (IARC/WHO 1991). Work on arsenicals saw the introduction of Paris green in 1867. This impure copper arsenite became so widely used to control the spread of Colorado beetle that by 1900 legislation had been enacted in the US to regulate its application. The early twentieth century saw the development of a number of other chemicals. Many, such as creosote, anthracene and naphtha, were based on tar oils.

But it was the period during and following the Second World War that first saw the intensive development of synthetic insecticides. While 1,1,1-trichloro-2,2'*bis*(*p*- chlorophenyl)ethane (DDT) was first synthesised in 1874, its action as an insecticide was not discovered until 1939. DDT was released commercially in August 1945, having been used during the war for protection of military areas and personnel. The availability of such an effective and cheap insecticide heralded an agricultural revolution reflected in the phenomenal growth in pesticide production. In 1944 total world DDT production was limited to 4366 tonnes. By 1963 production within the US alone had peaked at 81,154 tonnes (WHO 1979).

By the late 1960's, DDT was credited with the eradication of malaria from the United States and Italy (Attaran and Maharaj 2000). However, following environmental concerns (see

below), by 1970 use in the US had dropped to 11,316 tonnes, although use in Australia remained high on a per capita basis at 1000 tonnes (compared with Canada 287 tonnes and West Germany152 tonnes).

The 1940's also saw the discovery of most of the major families of insecticides still in use at the end of the century- organophosphates, carbamates and other organochlorines such as chlordane. Until the 1960's however, DDT remained by far the most widely used insecticide throughout the world.

During the 1970's and 1980's, many new insecticides were introduced, including the synthetic pyrethroids developed from naturally occurring pyrethrins. Increased knowledge about host-pest interactions also allowed new formulations and methods of application, and a large number of new chemicals were developed within each family.

By 1985 the explosion in pesticide use had created a total world insecticide market estimated to be worth over $US 4billion. Most insecticide use is targeted at agricultural production, especially of pesticide dependant crops such as cotton (accounting for almost one quarter of world insecticide production), rice, maize, soya beans, wheat and tobacco. Approximately 10% of world pesticide use is aimed at public health programmes, largely relating to mosquito control in developing countries.

Unfortunately, further experience with DDT demonstrates that the widespread use of pesticides can have negative as well as positive effects (WHO 1979). Part of the success of DDT, the first widely used synthetic pesticide, can be attributed to its persistence in the environment, thus reducing the need for frequent application. This chemical stability and an associated lipophilicity result in DDT and other organochlorines being readily stored in, and only slowly eliminated from, most living creatures. A large number of organisms, in particular marine filter feeders, can also act as bioconcentrators creating levels of DDT in their own flesh above ambient environmental concentrations.

Organochlorine pesticides also have the capacity to accumulate through the food chain, in particular in predatory animals at the top of the ecological pyramid. In the late 1960's, dead Sea Eagles in the Baltic and North Sea areas were recorded with up to 36,000 ppm of DDT in pectoral muscle (Jensen 1969). Human biological sampling also showed increasing DDT levels in almost all human communities, mainly due to exposure to residues in food. By the mid 1950's DDT could be detected in most foods and daily exposure in the US had been estimated at 0.184 mg per man per day (Walker, Goette et al. 1954). Following restrictions on the application of DDT to livestock and forage crops, as well as on crops directly eaten by man, there was a gradual decrease in residues in animal and vegetable foods. By 1964, DDT intake in the US was estimated at 0.038 mg per person per day (Durham, Armstrong et al. 1965). National surveys by the US Food and Drug Administration showed levels falling to 0.015mg/man per day by 1970 (WHO 1979).

While contaminated food posed the greatest route of human exposure to DDT, the general community was also exposed through other media. In 1975, three years after DDT was withdrawn from use in the United States, it could still be widely detected in air in the Mississippi Delta (Arthur, Cain et al.). Nor was agricultural use the only source of environmental contamination. Effluent from the Montrose chemical plant in California, near Los Angeles was discharged into the main city sewer, which, in turn, emptied into Santa Monica Bay. From 1953 to 1971 an estimated 270kg per day of DDT was released into the marine environment, with resulting residues detectable in ocean creatures over an area of more than 10,000km^2 (Ramade). Indeed, almost no part of the globe has escaped contamination with these persistent chemicals. While these substances have never been used in the Antarctic, ice cores taken from the Antarctic shelf show detectable levels of DDT and other organochlorines (WHO 1979).

The first studies of potential adverse effects of organochlorine insecticides were made in the mid-1950's. In 1956, DDT added to the feed of pheasants was found to cause a decline in the number of eggs laid and the viability of chicks (Ramade). In the mid-1960's the first suggestions were made that this might be having an impact in the broader environment. In a comparative study of samples of eggs conserved in different British museums, it was found

that the ratio of eggshell weight to the axial length of the egg in peregrine falcons decreased suddenly between 1945 and 1946, years, which saw the introduction of DDT on a large scale (Ratcliffe 1970).

At the same time adverse effects were becoming obvious in wild animal populations. Examples include the virtual disappearance of the Coho and Kiyi salmon from Lake Michigan (the eggs and small fry of fish are particularly sensitive to organohalogen compounds, with a concentration of 5ppm DDT in water resulting in 48.3% mortality of carp embryos in the egg) (Ramade). Contamination of their prey with insecticides and PCB's was also the main cause of a dramatic decline in numbers of fish eating birds including the peregrine falcon and osprey.

The main impact of contamination appeared to be on reproductive success. For example the Conetticutt colony of osprey had fallen from 150 breeding pairs in 1952 to 5 pairs in 1970 with an average of 0.23 fertile young per nest, far below the number required to maintain the population. Perhaps the most spectacular case that can be directly ascribed to organochlorine pollution is that of colonies of the brown pelican (Blus, Cromartie et al. 1979; Ramade 1987). Colonies in islands off southern California dropped from 3000 breeding pairs in 1960 to only 300 in 1969. Among remaining pairs at that time, 1200 eggs were laid, but only 5 viable chicks were born.

The relationship between organochlorines and eggshell thinning and impaired fertility in birds was confirmed experimentally in ducks, and is thought to be due to changes in calcium metabolism (Lehner and Egbert 1969; Peakall 1969). A causal relationship is also supported by recent research in the US that indicates an increase in eggshell thickness of nearly 50% in some bird species since the withdrawal of DDT (Burger, Viscido et al. 1995).

However, the devastating environmental impact of DDT remained mainly of academic interest until 1962, when public concern was aroused by the publication of "Silent Spring" which sold nearly a million copies in less than two years (Carson 1962). The President's Science Advisory Committee noted, "until the publication of *Silent Spring*, people were generally

unaware of the toxicity of pesticides"(Lear 1999). The controversy arising from the ensuing public debate ultimately led to a raft of legislative initiatives. These included the withdrawal of DDT from use in the US, and the establishment of the United States Environmental Protection Agency in 1969. These concerns also led to a large number of studies investigating whether exposure to these substances might adversely affect human health.

2.2 HEALTH EFFECTS OF INSECTICIDES IN HUMANS

2.2.1 Acute Pesticide Poisoning

It is widely reported that most pesticide related deaths involve acute poisonings rather than chronic exposure (WHO/UNEP 1990). As pesticide use has become more widespread, mathematical models have estimated increasing numbers of pesticide poisonings throughout the world, rising from 500,000 cases/yr in 1972 to 25,000,000 cases/yr in a 1990 estimate, though only a small percentage of deaths are identified and reported. 148 poisoning outbreaks were reported between 1951 and 1990, involving 24,731 cases and 1065 deaths, with food being the most common route of exposure. Two countries, the United States and Thailand, accounted for more than half the reports, probably reflecting the quality of their notification systems.

In the US, a descriptive analysis of national mortality data, National Hospital Discharge Survey data, and American Association of Poison Control Centers national data from 1985 to 1990 found 341 fatalities from agricultural and horticultural chemicals over the 6-year period, of which 64% were suicides, 28% were unintentional, and 8% were of undetermined intent (Klein-Schwartz and Smith 1997). 25,418 hospitalizations were reported, 78% identified as unintentional. Both deaths and hospitalizations occurred more frequently in males, and rates were higher in nonwhites than in whites. 338,170 poison exposures were reported to poison centers for fungicides, herbicides, insecticides, and rodenticides, with life-threatening manifestations or long-term sequelae occurring in 782 cases, and 97 deaths reported.

2.2.2 Background to Studies on Chronic Health Effects

Epidemiologic research into the health effects of chronic pesticide exposure is plagued by many problems (Blondell 1990). Foremost among these is difficulty getting accurate information on subject exposure. Exposures to pesticides in the general community are low and heterogeneous. To explore possible adverse impacts of pesticides, researchers have therefore frequently turned to occupational studies, where exposures are likely to be higher and more predictable.

However, even in an occupational setting, pesticide exposure tends to be difficult to assess. Only workers involved in the *production* of pesticides operate in typical industrial settings where workers are indoors, the environment is relatively stable and environmental monitoring may allow an estimation of subject exposure.

On the other hand, pesticide *users* rarely have standardised work practices (Alavanja, Sandler et al. 1999). Users are often either self-employed or members of family businesses, and generally work in environments that vary markedly from minute to minute depending on the task at hand. Users may apply a range of pesticides for different purposes and may mix as well as apply.

Where biological monitoring has been undertaken in pesticide users, it has often been limited to monitoring of biological effect such as serum cholinesterase levels, rather than measuring internal exposure dose (Wooler 2000). While biological monitoring for persistent pesticides such as the organochlorines can give a meaningful picture of total exposure over a number of years, metabolism and excretion of more modern pesticides is rapid and results of biological monitoring may only reflect exposure in the last few hours or days.

In the absence of meaningful information on individual exposures, researchers have often turned to simple occupational categorisation. To be most effective, such an approach requires homogeneity in the exposures likely to be experienced by subjects identified in each category. Where, for example, categories such as “farm hand” are identified from census or other routinely collected documents, heterogeneity of exposure lessens the ability of these studies to

detect true associations. More accurate indications of occupational exposure can be developed when subjects are drawn from a single employer or setting, however even these may be misleading.

Some of the issues around exposure assessment were examined by a review of studies of the possible effects of dioxin contaminated "Agent Orange" used by military personnel during the Vietnam War (Wolfe, Michalek et al. 1995). A number of large studies have been unable to lead to agreement on a possible association between Agent Orange exposure and a range of reproductive outcomes including spontaneous abortion and birth defects.

One key methodological problem related to exposure assessment. Until 1992, exposure assessment in subjects was limited to military service in Vietnam as a surrogate for Agent Orange exposure. Sometimes this was supplemented by subjects' own estimate of exposure, or indices developed by researchers estimating the likelihood of exposure. However, in 1992, the Air Force released results of the first study to examine the relationship between individual serum TCDD (the dioxin contaminant of Agent Orange) and verified reproductive outcomes. Interpretation of the results of this study is complex, but personnel involved in the handling of Agent Orange were, indeed, shown to have significantly higher TCDD levels than controls (median 12.8 pg/g and 4.2pg/g respectively). However, these levels correlated poorly with both self reported exposure and exposure indices developed from military records.

These findings confirm the potential bias in results generated by research dependant on these surrogate measures, and the need for a degree of scepticism when interpreting their findings.

Another problem for epidemiological studies exploring the health impact of pesticides relates to selection of controls. A widespread problem in occupational health is the "healthy worker effect". This is characterised by the tendency for relatively healthy individuals to be more likely to gain employment and remain employed (McMichael, Andjelkovich et al. 1976). This may potentially bias studies towards finding lower mortality rates in an occupational cohort when compared with the general community and thus mask true increases in mortality. The

impact of the healthy worker effect can be seen in many of the occupational studies discussed below.

The healthy worker effect may be exacerbated by the unique dietary and lifestyle factors associated with residence on a farm. For example, farmers are less likely to smoke, more likely to eat local produce, more likely to be exposed to petrochemical products, exhaust fumes, mineral and organic dusts, and to face biological exposure to animals and microbes. In general, residence on a farm is thus also associated with mortality and cancer rates below those in the broader community (Ritter, Wigle et al. 1990).

A more general epidemiological problem faced by these studies is determining subject outcome. Most large studies have focussed on defined endpoints such as mortality. In general, these have relied on death certificates for outcome data, causing a loss of study precision since death certificates are, in practice, poorly completed. This is exacerbated by difficulties matching subjects with deaths and cancer registries, particularly in developing countries where data collection may be less comprehensive.

Finally, a range of other factors may confound the relationship between pesticide exposure and cancer mortality. These possibly include smoking, carcinogenic animal viruses (leukaemia), and the lymphoproliferative effect of prolonged antigenic stimulus (multiple myeloma and other haematological malignancies). Our understanding of both these groups of risk factors is currently limited and inconsistent (Pearce and Reif 1990).

2.3 DESCRIPTIVE AND ECOLOGICAL STUDIES

A number of studies have been undertaken using geographic indicators as surrogates for exposure. While useful for suggesting possible adverse outcomes and for generating hypotheses, these "ecological" studies suffer from a number of common weaknesses relating to exposure misclassification.

A typical ecological study examined the relationships between mortality data for cancers of the brain, lymphatic tissue and leukaemia, and the spatial distribution of agricultural pesticide use for 34 drainage basins in Quebec, from 1976-1985 (Godon, LaJoie et al. 1991). The basins were grouped into three categories (low, intermediate, and high exposure) according to the level of sales of pesticides. For cancers of the lymphatic tissues among women 35 to 64 years of age, a high relative risk (RR) was observed (RR = 1.91, 95% CI 1.14-3.18) in basins highly exposed to pesticides compared to those with low exposure. Analysis of correlation for this cancer at 34 basins showed significant associations between geographical distributions of the Standardized Mortality Ratio and those of numerous variables indicative of pesticide use in agriculture.

Another Canadian report highlights some of the difficulties inherent in ecological analysis. This project investigated the mortality of approximately 70,000 male Saskatchewan farm operators, a subset of a larger group of 365,000 Canadian farm operators investigated separately (Ritter, Wigle et al. 1990). Analysis indicated that during the study period, overall mortality among Saskatchewan farmers was 25% lower than that for all Saskatchewan men. During the same time interval, the risk of death from all types of cancer was also about 25% lower among Saskatchewan farmers than for all Saskatchewan men. As discussed previously, these results restate a common finding in studies looking at the health of farmers. However, the study did identify a relationship between non-Hodgkin's lymphoma mortality and acres sprayed for weeds and concluded that the magnitude of risk for Saskatchewan farmers was probably greater than that reflected in the estimates in the study, due to the likelihood of misclassification of exposure. Non-Hodgkins Lymphoma has been associated with herbicide use in a number of other studies (see below), lending weight to these findings.

Mortality rates were investigated in three rural municipalities (population 96,000) in the Philippines before (1961-71) and after (1972-84) the widespread use of organophosphate and organochlorine pesticides (Loevinsohn 1987). Deaths from pesticide poisonings increased significantly. For men aged 15-54 years, the mean age-standardised mortality rate for all cancers (except brain) increased from 21.1 to 25.9, although this was not significant. Mortality from leukaemia in men increased from 0.6 to 3.6 per 100,000 ($p<0.05$). Leukaemia

rates for women for the same periods were 0.6 and 0.7 per 100,000, respectively. Unfortunately, exposure classification in this study was crude, and the comparison between different time periods introduces the potential for confounding by other factors such as impoverishment, increasing use of tobacco and changing reporting habits.

Computerized mortality listings for Wisconsin for 1968-1976 were used to compare death and cancer rates in residents with an occupation identified on death certificates of "farm owner", "tenant" or "labourer", with white, non-farming Wisconsin men (Blair and White 1981; Saftlas, Blair et al. 1987). Data from agricultural and population censuses were used to construct indicators of exposure. Among all Wisconsin farmers, significantly decreased proportional mortality ratios were seen for tobacco- and alcohol-related causes of death, while excesses occurred for accidental causes, asthma, and cancer of the stomach, prostate, eye, and lymphatic and haematopoietic systems. Elevated proportional cancer mortality ratios (PCMR's) for leukemia, all lymphopoietic cancers and cancers of the stomach, rectum and eye occurred in farmers born 1905-1958, while deficits were observed for cancer of the pancreas and the category "all other cancers." Increases in PCMR's with level of various agricultural activities were largely associated with cancers of other lymphatic tissue (2/3 of which were multiple myeloma) and the rectum. No positive PCMR gradients were observed for leukemia and malignancies of the stomach and eye.

In a separate, but related, study, 774 subjects identified from digitised Wisconsin mortality listings were compared with controls dying from other causes. Younger farmers in counties with high agricultural activity determined from agricultural census had an elevated risk for reticulum-cell sarcoma (Cantor 1982).

One of the weaknesses of this and similar studies is reliance on information from death certificates. Even if the cause of death is accurately identified and the recorded occupation at the time of death is correct, no information is available on previous employment. In these studies, farm owners, tenants, foremen and labourers were all classified as farmers, although many of these may not have been actively engaged in farm work. Exposure to insecticides

was estimated by the agricultural characteristics of the county and may not reflect individual exposure. Such problems can result in a bias toward the null.

Another study assessed the contribution of vineyard pesticides to brain cancer mortality among agricultural workers (Viel, Challier et al. 1998). A pesticide exposure index (PEI) in vineyards was calculated for 89 French geographical units (departements). The authors identified male farmers and farm labourers aged 35-74 from national death data for the years 1984-1986. Brain cancer mortality among these subjects (using census data to identify total numbers of farmers and estimate rates) was compared with that for the general population. Mortality from brain cancer among farmers was significantly higher than mortality for the overall population (standardized mortality ratio = 1.25, $p < .001$) and univariate and multivariate analysis accounting for economic status as a confounder revealed a significant link with pesticide exposure in vineyards (RR 1.11; 95% CI 1.03-1.19). The accuracy of these findings is dependant on the "usual occupation' stated by relatives of the deceased and since no cancer registry exists in France was limited to mortality which may also be influenced by other factors such as health service utilisation or access. The exposure index was estimated for 1970 and based largely on the proportion of usable agricultural land devoted to vineyards.

Several case control studies have used ecological methods to examine possible associations between insecticides and specific cancers (Cocco and Benichou 1998). One such study examined the relationship of prostate and testicular cancer mortality with environmental exposure to the DDT metabolite p,p'-dichlorodiphenyldichloroethylene (DDE), a known anti-androgen, during the period 1971-1994. Environmental DDE contamination by state was estimated by measuring DDE concentrations in the subcutaneous fat of population samples and by measurements of DDE in tree bark. However, sampling numbers were small, and representativeness of fat and tree samples was not determined. Neither prostate cancer mortality nor testicular cancer mortality showed a positive association with either indicator.

The relative risk of prostate cancer in farmers was also estimated in a meta-analysis from articles published in peer-reviewed journals between January 1983 and June 1994 (Keller-Byrne, Khuder et al. 1997). Positive associations between prostate cancer and farming were

found by analysis both for all studies and analysis limited to retrospective studies. No association was found with analysis that included only studies reporting a standardised mortality ratio. These findings may have been influenced by selection bias since negative studies may have been less likely to be reported in peer-reviewed publications. The meta-analysis also did not distinguish between well-designed studies and those compromised by methodological flaws. However, many of the studies included were looking at multiple cancer sites and there was no temporal trend in risk estimates, which might be expected if publication bias were influencing the findings. One plausible explanation for the positive association between prostate cancer and farming is exposure to hormonally active agricultural chemicals. However, a number of lifestyle factors apart from pesticide exposure could also explain the observed association with prostate cancer. These include dietary fat consumption, exercise and exposure to micro-organisms found in cattle.

Another possible effect of hormonally active chemicals could be reproductive disturbances. A Norwegian study compared the perinatal health of 192,417 children born to parents identified by agricultural census as farm holders, with 61,351 births to non-farmers in agricultural municipalities (Kristensen, Irgens et al. 1997). Subjects were matched with the Medical Birth Registry of Norway, which comprises all births with more than 16 weeks of gestation. One of the strengths of this study is the completeness of these national records. Perinatal mortality between the two groups was similar, but the proportion of late-term abortions (gestational weeks 16-27) was higher among farmers' births (odds ratio (OR) = 1.9, 95% confidence interval (CI) 1.6-2.3). The increase in late-term abortion among the farmers could to some extent be attributed to an excess of mid-pregnancy deliveries among grain farmers. The authors concluded there was no convincing evidence that perinatal death was associated with use of pesticides. However, the results did support the hypothesis that occupational exposure to mycotoxins in grain induces labor at an early stage of pregnancy.

A case-control study of multiple myeloma among males was conducted with the use of digitized mortality listings for 1968-76 from the State of Wisconsin (Cantor and Blair 1984). Age, year of death, race, county of usual residence, marital status, and usual occupation were available for the 411 male deaths due to multiple myeloma and for a matched series of deaths

due to other causes. Controls dying from tobacco related causes were excluded to minimise bias created by differences in smoking patterns between farmers and other occupations. Farmers were at an elevated risk compared to non-farmers (odds ratio (OR) = 1.4), with decedents 65 years of age or older having a stronger association (OR = 1.5) than younger farmers (OR = 1.1). County levels of selected agricultural characteristics were used as surrogate measures of exposure. Significantly elevated odds ratios were observed for farmers residing in counties high in chicken inventory (OR = 1.6), fertilizer use (OR = 1.7), and acres treated with insecticides (OR = 1.9). As with similar studies, indirect exposure measures and reliance on death certificates for case identification potentially bias this study. On the other hand, excluding controls dying from tobacco related disease minimises problems arising from lower smoking rates in farmers.

Other ecological studies have also suggested a link between predicted pesticide exposure and death rates from multiple myeloma and leukaemia. Census and deaths data was used in a study of the French farm labourer population aged 35-74 in 89 "departments" for the period 1984-1986 (Viel and Richardson 1993). SMRs were calculated using national rates. Rates were high for multiple myeloma (SMR 1.59; 95%CI, 1.32-1.89) and leukaemia (SMR 1.33; 95% CI 1.19-1.49), but not lymphoma. Leukaemia was also significantly associated with a calculated geographical pesticide exposure index.

An early ecological study examined the risk of leukemia among farmers using records of death certificates from Nebraska, 1957-1974 (Blair and Thomas 1979). Comparison of occupation, as recorded on the death certificate, for 1084 leukemia deaths and 2168 deaths from other causes, matched for age at death, year of death, county of residence, race, and sex, revealed an elevated risk of leukemia among farmers (OR, 1.64; 95% CI, 1.18-2.27). The risk was increased among farmers born after, but not before, 1900 suggesting a relationship with agricultural exposures of recent origin. Stratification by county of residence showed a significantly elevated risk for farmers from heavy corn producing counties.

In summary, results from ecological studies are inconsistent and subject to a number of potential biases. Associations identified in these studies that may be worth further

investigation include leukaemia, prostate cancer, brain cancer, lymphopoietic cancers, multiple myeloma, and perinatal mortality.

2.4 COHORT STUDIES

One of the major strengths of cohort studies is that they generally include the total available study population. They also take place in the "real world", and follow the traditional experimental strategy of following exposed and non-exposed groups over time to identify adverse health effects. The International Agency for Research on Cancer has identified over 40 established human carcinogenic agents. For 58 percent of these, a cohort study was the main type of evidence on which causality was established (Breslow and Day 1987).

However, cohort studies in general, and in the field of pesticide exposure in particular, have a number of failings. Prospective cohort studies require large study numbers and long follow-up periods for even relatively common outcomes. For example, most cancers, even the more common types such as lung or colon cancer, occur at rates in the order of 5-100 per 100,000 persons per year (Tomatis, Aitio et al. 1990). In industries such as agriculture, where many itinerant workers may be employed, follow-up of prospective studies may be difficult and subject to bias, since the most mobile worker groups may be the least familiar with accepted practices and face the highest exposures.

Historical cohort studies often allow prolonged periods of follow-up, since the cohort may have been defined many years in the past. However, such studies are often limited by the availability of data and the loss of subjects to follow-up. As discussed previously, estimation of exposure for study populations is also likely to be a problem, especially when exposures may have occurred at some time in the past, or in unregulated conditions. Historical cohort studies also tend to be limited to the investigation of fatal diseases since this is the only information routinely collected in many countries. The investigation of non-fatal outcomes may require considerable effort and, when available, is limited by the need for morbidity data

from comparable non-exposed populations and often by the limitations of self-reporting by subjects aware of their exposure classification.

A number of cohort studies have either not been able to demonstrate any convincing adverse outcomes from pesticide exposure, or appear to identify a protective effect (Littorin, Attewell et al. 1993; Amoateng-Adjepong, Sathiakumar et al. 1995) (Faustini, Forastiere et al. 1993; Torchio, Lepore et al. 1994). Even though some of these studies are large and include significant follow-up periods, they generally compare outcomes in the study cohort with those in the general community. The possible influence of the healthy worker effect and validity of using the general public as the reference population need to be considered when interpreting these results. Similarly, accurate ascertainment of vital status and cause of death in the study population is important, since failure to identify all deaths (or other outcomes such as cancer) in subjects will bias a study toward finding rates that are below the general population.

Even studies with positive findings for a specific outcome often report total mortality and cancer rates below those in the reference population. Since a large number of possible outcomes are often investigated in each study, these "significant" findings may be the result of chance alone. However, since these study cohorts may be intrinsically healthier than the reference population, these findings may, in fact, conceal a number of other true associations and underestimate the real degree of risk for those positive associations that are identified.

Cohort studies investigating pesticide exposure have generally been based in a number of recurring settings: pesticide manufacturing and formulation plants, pesticide applicators, farmers, gardeners and grain millers.

2.4.1 Pesticide manufacturers/formulators

Traditionally, pesticide manufacture has occurred in large plants with a relatively stable workforce, although this may have changed over recent years with significant manufacturing of agrichemicals now occurring in third world countries. However, exposures at these plants have generally been considered to be lower than at formulating plants and to also include both chemical precursors of the final technical grade pesticide, or other pesticides manufactured at

the same facility. Formulating plants tend to be smaller operations, with a seasonal workforce, high turnover rate, higher exposures to multiple chemicals, and poor records (Ditraglia, Brown et al. 1981).

A study of 570 workers employed between 1 January 1954 and 1 January 1970 either in a production or formulation plant for the organochlorines Aldrin and dieldrin highlights some of the strengths and weaknesses of such investigations(de Jong, Swaen et al. 1997). Atypically, there were extensive industrial hygiene data available as well as biological monitoring data for most of the workers, allowing individual estimates to be made of the total intake of dieldrin. Subjects were followed up for mortality until 1 January 1993. A total number of 2539.37 person-years at risk were added to an original study that had previously suggested an increase in liver cancer. 118 deaths were observed compared with 156 expected. No increase in mortality from liver cancer was found. However, there was an excess in mortality from rectal cancer. This excess was inversely related to the dose gradient. An analysis by job title did not show any excess cancer in any particular job and the study concluded that the results did not support a carcinogenic effect of dieldrin and Aldrin in humans. The major strength of this study lies in the excellent exposure data available. However, comparison was limited to the general population, thus potentially biasing the study to the null due to the "healthy worker effect", study numbers were small, follow-up limited, and outcomes were restricted to mortality.

Another study of workers employed in the manufacture of chlorinated hydrocarbon pesticides (DDT, chlordane, heptachlor, and Aldrin/Dieldrin/Endrin) defined a cohort of 2,100 workers employed in one of four manufacturing plants for at least six months prior to January 1964 (Ditraglia, Brown et al. 1981). Vital status ascertainment for these cohorts ranged from 90 to 97% complete and follow-up continued until 31 December 1976. Death certificates were obtained for all subjects known to be deceased. Those with unknown vital status were assumed to have survived until the end of the study. Standardized mortality ratios (SMR) for all causes ranged from 66 to 82. For total cancers the SMRs ranged from 68 to 91 and for respiratory cancer from 55 to 132. In the Aldrin/Dieldrin/Endrin cohort observed deaths due to pneumonia and "other respiratory diseases" were significantly above the expected number of

deaths. However, the study is weakened by low power, limited follow-up period, and comparison with the general population. In addition, analysis does not appear to have included a lag period. Since it is likely that many conditions will only result in death some years after initial exposure, including this intervening period in analysis can bias results.

This study was later updated with follow-up continuing until December 1987 (Brown 1992). The mortality for all causes and all malignant neoplasms at each of the plants remained lower than expected. However, a statistically significant increase in liver and biliary tract cancer among workers at one plant was observed (5 observed, SMR 3.93, 95% CI 1.27-9.20). Overall mortality from liver and biliary tract cancer was also non-significantly elevated. These results were somewhat consistent with experimental animal findings showing benign and malignant tumors of the liver after exposure to Aldrin and Dieldrin. However, deaths were due to a mixture of intra- and extra-hepatic tumors, and the dose-response analysis was limited because of the small number of deaths and lack of exposure data. Stomach cancer was raised, though non-significantly, at three of the four plants, and cerebrovascular deaths were also raised at three of four plants (one significant).

Another study of United States workers involved in the production of DDT and other chemicals followed 3579 men for the period 1935-1976 using employment and social security records (Wong, Brocker et al. 1984). 5.4% of subjects were lost to follow-up and death certificates were found for 94% of deaths. SMRs were determined against the US white male age-cause-specific mortality rates for the same period. The overall mortality rate was significantly lower than for the US population, and SMRs for circulatory disease, non-malignant respiratory disease and diseases of the digestive system were also reduced. Death rates from diabetes were raised for the whole cohort, as were rates for respiratory cancers in workers exposed to DBCP. No causes of death were significantly elevated for subjects exposed to DDT but the sub cohort only comprised 740 subjects.

2.4.2 Pesticide applicators

A number of studies have been undertaken among licensed pest control operators for whom records may be broader and better maintained than for unlicensed, and often itinerant,

agricultural staff (Thomas, Winter et al. 1996). A typical prospective mortality study involved the follow up to the end of 1994 of 1485 male pest control officers aged between 17 and 69 and employed in 296 local authorities in England and Wales for at least six months between January 1980 and April 1984. 200 deaths occurred during the follow up period of which 65 were due to cancer. Observed numbers of deaths were compared with those expected on the basis of the rates for relevant calendar year, cause, sex, and age specific groups for England and Wales. No tumour type showed significantly more deaths than expected. Total all cause, lung cancer, and respiratory disease mortality were significantly lower than expected. These negative findings are likely to have been influenced by the healthy worker effect and limited duration of follow-up.

A similar, but smaller, study examined the mortality of a cohort of 168 pesticide applicators employed by the city of Rome for an average of 20 years (Figa-Talamanca, Mearelli et al. 1993). Exposure data were obtained from work records, and causes of death for the 42 workers who had died, were obtained from death certificates. Standardized mortality ratios (SMR) for specific causes of death were computed on the basis of provincial mortality rates. An excess in mortality from cancer of the liver and bile ducts with four cases observed and 0.7 expected (SMR = 571, 95% confidence interval (CI): 154-1463) was found. Increased risk for other cancers was also observed, but the SMRs were not statistically different from unity. An increased risk of liver cancer occurred in those exposed to organochlorine pesticides between 1960 and 1965. While exposure data for this study is relatively accurate, it is limited by very small numbers and a short follow-up period, as well as comparison to regional norms.

A larger cohort study of pesticide applicators in Rome followed a cohort of 2310 male workers who obtained a licence in the period 1973-1979 (Figa-Talamanca, Mearelli et al. 1993). The vital status of the cohort was determined up to the end of 1988, providing a maximum 15 years of follow-up. The causes of death of the 207 who had died were ascertained from local population registries and telephone interviews. Cause of death was determined from death certificates. Standardized mortality ratios (SMR) were computed using national mortality rates. SMR for all causes was 56 (95% confidence interval (CI): 45.3-59.8), for cardiovascular diseases 47 (95% CI: 37.1-59.1), and for all cancers 72 (95% CI: 57.8-89.3). A

statistically significant excess was noted for brain cancer (SMR = 270, 95% CI: 108.6-556.9). In addition, the cohort experienced statistically significant lower lung cancer mortality (SMR = 57, 95% CI: 35.6-80.0). This study has been criticised for a number of potential biases including the exclusion of 31% of deaths because of incomplete information, lack of histological confirmation and the lack of exposure information (Bohnen 1994). The study was limited by the short follow-up period, and the low SMR for all deaths (below that experienced in similar studies of farmers) suggests there may have been a problem with ascertaining vital status. Loss to follow-up was not specified.

An early cohort study of pesticide exposed workers compared deaths and responses to questionnaires from survivors in 2,620 pesticide exposed workers and 1,049 "controls", recruited in 1971-73 (Morgan, Lin et al. 1980). 72% of exposed subjects and 75% of controls were accounted for either by returned questionnaire or mortality. Deaths were followed for the period 1971-1977. Disease incidence rates were studied in relation to broadly defined occupational subclasses, and to serum concentrations of organochlorine pesticides (OCs) measured at the time of recruitment. Death by accidental trauma was unusually frequent among pesticide applicators. Mortality from cancer and arteriosclerosis were not significantly different from those observed in the controls. Among survivors, dermatitis and skin cancer were unusually common in structural pest-control operators. Internal cancer was no more frequent in the intensively pesticide-exposed workers than in the controls, but it appeared to occur at an unusually high rate in workers characterized as "possibly pesticide-exposed". There were apparent associations between high serum pesticide organochlorine levels measured in 1971-73 and the subsequent appearance of hypertension, cardiovascular disease, and possibly diabetes. While this study has the advantage of a comparable reference group, the follow-up period was small. Reporting bias is also possible since information was largely self-reported and the loss to follow-up was large.

In Sweden, 20,025 pesticide applicators in agriculture licensed between 1965-1976 were followed in the Cancer Register using a unique personal identification number from date of licence until death or December 31, 1991 for a mean follow-up period of 21.3 years (Dich and Wiklund 1998). During approximately 400,000 person years of follow-up 401 cases of prostate

cancer were observed compared to 355 expected, with a standardized incidence ratio (SIR) of 1.13 (95% confidence interval: 1.02-1.24). There were 7 cases among those born in 1935 or later, and the SIR was 2.03 (0.82-4.19). For those born earlier than 1935 the SIR was 1.12 (1.01-1.24).

Deaths in a US a cohort of 16,126 males employed for three months or more by any of three US pest control companies between 1967 and 1976 were identified by a search of Social Security Administration records (Wang and MacMahon 1979). Only a small percentage of subjects were black, and exposure classification was limited to "job categories potentially involving exposure to pesticides". Overall, 311 deaths were ascertained, giving a standardized mortality ratio (SMR) of 84. However, death certificates could not be found for 42 of these cases. The reliance on Social Security records as a measure of vital status also introduced the potential for under ascertainment of deaths. The SMRs were over 100 for three causes of death--cancer of the lung (115), cancer of the skin (173) and cancer of the bladder (277). For lung and skin cancer these increases were not statistically significant. For bladder cancer the excess was on the border of statistical significance (p less than 0.05). There were significantly low SMRs for cancer of the digestive organs (46) and for other diseases of the digestive (55) and respiratory (29) systems. Deaths from cerebrovascular disease were also less than expected, though not significantly so. These findings are limited by the potential bias to the null due to under ascertainment of deaths, the Healthy Worker Effect, comparison of a largely white population with national rates, short follow-up and exposure misclassification. High mortality from lung and bladder cancer is suggestive of an effect of smoking and, as is typical in cohort studies of this sort, no information on smoking status was available on subjects.

This cohort was followed up approximately 10 years later and matched with Social Security Administration and National Death Index (NDI) files (MacMahon, Monson et al. 1988). Job histories were not updated. In all, 1,082 deaths were ascertained, and death certificates were obtained for 994 (92%), although for the period 1967-81 certificates were found for only 85% of deaths. The standardized mortality ratio (SMR) for all causes of death was 98. Although a number of specific causes of death showed SMRs significantly below 100, only one category of cause of death showed a significantly elevated SMR-cancer of the lung, with an SMR of

135. Termite control operators (TCO), the group with the greatest likelihood of exposure to organochlorines, had an SMR for lung cancer of 97, compared with 158 for other pesticide operators. The authors believed the likelihood of this association with lung cancer being real was lessened by the observation that the excess of lung cancer in the non-TCO workers was limited to operators employed as such for less than five years. However, no data was available on type or duration of employment beyond 1977, and only a limited number of subjects were employed for more than five years. It is also possible that exposure during the first years of employment may be higher than at other times due to inexperience and new workers being given less pleasant jobs. While the second phase of this study benefits from longer duration of follow-up, some of the potential for bias to the null described for the parent study remains.

2.4.3 Agricultural Workers and Farmers

Since agricultural workers are generally employed at a diverse range of sites and experience a heterogeneous pattern of exposure, defining a cohort based on agricultural exposure is usually more difficult than for licensed pesticide operators. A meta-analysis of studies of cancer rates in farmers found excess cancer risks for Hodgkin's disease, multiple myeloma, leukaemia, melanoma, and cancers of the lip, stomach and prostate, with non-significant increases noted for non-Hodgkin's lymphoma and cancers of connective tissue and brain (Blair, Zahm et al. 1992). Statistically significant deficits in risk occurred for all causes of death, ischaemic heart disease, all cancers combined and cancers of the lung, oesophagus, bladder, colon, liver, and kidney. The approach used in this study weighted the contribution of each investigation equally, and adjustment could not be made for a number of potential biases including the "healthy worker effect". Many of these studies are also biased to the null merely by the limits of exposure classification. For example, if only 40% of farmers used a specific chemical that doubled the risk of disease compared to non-using farmers, a study using classification of "farmer" as its exposure measure would only yield a relative risk of 1.4.

One Norwegian study established a cohort of farm holders and their spouses identified from agricultural censuses in 1969-1989 and linked to the Central Population Register (Kristensen, Andersen et al. 1996). Available census information on the activity of the farm provided the

exposure indicators. Subjects were followed up in the Cancer Register from the census year they were first identified until 1991. 91.5% of women were followed up for less than 5 years. 75.7% of men were followed up for less than 12 years. In an analysis for standardized incidence ratios (SIR), the cohort was compared with the total rural population of Norway. In the follow-up of 136,463 men for 1.5 million person-years and 109,641 women for 0.6 million person-years, 3333 and 2145 cancer cases were identified, respectively. The subset defined as farmers had an SIR of 77 (95% CI, 73-81) for the men and 92 (95% CI, 85-99) for the women, with particularly low SIR values for lung cancer and other sites linked to life-style. Only one cancer, leukaemia, had a significantly elevated rate in men (SIR 122, 95% CI 100-148), and this appeared to be limited to cattle farmers (rate ratio 1.76, 95% CI 1.02-3.05). Multiple myeloma was associated with pesticide indicators for both genders, mainly for subjects cultivating potatoes, and prostate and testicular tumours for orchard and greenhouse workers. This large study is limited by short follow-up periods, particularly for women. Given the lag time necessary for cancer development, this may bias the findings towards the null.

A similar study was undertaken in Canada where the records of 156,242 male Alberta, Saskatchewan and Manitoba farmers identified on the 1971 Census of Agriculture were linked to the corresponding Census of Population records and the Canadian Mortality Data Base (Morrison, Semenciw et al. 1992). A total of 228 cases of brain cancer were identified which were then linked to the Canadian National Cancer Incidence Database and Provincial Cancer Registries for histological information. Exposure indices for individual farm operators were derived from 1971 Census records. Standardised mortality ratios were calculated for the period 1971to 1987 using external age-specific mortality rates. All cause and all cancer mortality rates for male farm operators were significantly below those for the provincial population (SMRs 0.72 and 0.77 respectively). The authors reported this was likely to reflect the “healthy worker effect”, low smoking rates among Canadian farmers, and failure to identify all deaths in the mortality database (10-15% of all deaths were estimated to have been missed). Matching of cohorts to mortality registries is difficult since names and dates of birth may be recorded differently or incorrectly at cohort entry or death registration and the resultant bias to the null is common in registry dependent cohort studies. Brain cancer mortality was similar to the wider community (SMR 0.98; 95%CI 0.80, 1.05). A nested case-

control study was undertaken comparing a range of variables with outcome. A statistically significant association was noted between risk of dying of glioblastomas and increasing fuel/oil expenditures (test for trend p = 0.03, top quartile relative risk = 2.11, 95% confidence interval = 0.89-5.01). No significant association was found between brain cancer and either education or mother tongue. However, low income was associated with a significantly reduced risk of brain cancer mortality.

Another study in farmers suggesting a possible association with brain cancer examined the mortality from 1974 to 1987of 4,580 male farmers licensed to buy and use pesticides in Northern Italy (Alberghini, Luberto et al. 1991). The historical cohort was determined from the registers of agricultural inspectorate offices. The vital status at the end of the study period was ascertained by municipality records and only 4 subjects were lost to follow-up. Death certificates were obtained for all of the 565 identified deaths. External comparison with the Italian male population was supplemented by regional comparison. Reduced SMRs were observed for all causes, all neoplasms and most specific malignancies including smoking elated neoplasms. A non-significant mortality excess due to brain cancer, compared both to national and regional populations, was found (11 cases, SMRs 169 and 139, respectively). This excess became statistically significant in the age group 65-75 years. Limitations of the study include absence of exposure information, healthy worker effect, short follow-up period and unspecified lag period.

Several countries, including Australia, have specific disease registries allowing the investigation of morbidity as well as mortality. Some of the difficulties faced by such studies are demonstrated by an historical cohort study of workers on banana plantations in Costa Rica (Wesseling, Ahlbom et al. 1996). Workers on the payrolls of banana companies, as reported to the Social Security System at any time between 1972 and 1979, were followed up in the cancer registry between 1981 and 1992. Databases of selected companies contained approximately 150,000 records, but there was a large amount of missing identification data. 38,000 records with adequate identification were selected and were matched against the Electoral Roll (ER) for 1992. The records of 33,482 subjects were found to have identical, or almost identical identification data and they were deemed to be alive for the duration of the

study. 4518 records that were not identified through the ER were then linked to the Mortality Register (MR). 887 subjects matched with deceased records. Standardised Mortality Ratios for all cause of death using this information was 53 for men and 56 for women. The authors believed this reflected a problem with identifying deceased workers and undertook a further linkage of the 3551 unmatched records against the Birth Register. This allowed the identity of a further 617 workers to be established of whom 515 were deceased and 102 alive in December 1992. A further 223 subjects were excluded because they could not get corroborating identification data from the Civil Registry. Thus the final study population comprised 29 565 men and 4892 women with 7.3% lost to follow-up. These were followed for a total of 407 468 person-years and were matched against the National Tumour Registry as well as the MR.

The observed cases of cancer were compared to the expected values, derived from national incidence rates. 368 cancer cases were identified, 292 among men (standardized incidence ratio (SIR) = 76, 95% confidence interval (CI) 67-84) and 76 among women (SIR = 116, 95% CI: 90-142). Among men increased SIR were observed for melanoma (SIR = 197, 95% CI: 94-362) and penile cancer (SIR = 149, 95% CI: 55-324); among women for cervix cancer (SIR = 182, 95% CI: 122-241) and leukaemia (SIR = 274, 95% CI: 86-639). Risk estimates for lung cancer were also elevated among male workers with the longest time of employment. These results need to be considered in the light of the considerable opportunity for selection and reporting bias. These are likely to have underestimated risk by limiting subject inclusion to those with complete identifying data, and death rates are likely to have been higher in those lost to follow-up. With numbers inadequate for internal comparison, the cohort's experience was then compared with the general population.

The study concluded that follow-up was difficult due to deficient identification variables in the cancer registry and to easier identification of the living compared to the deceased in the civil registry at the end of the observation period. The various systematic errors in this study were thought likely to produce an underestimation of the relative risk estimates. Such errors can potentially undermine many studies as matching of subjects with deaths and disease registries is never straightforward. Underestimates of death and disease rates are possible where names

and dates of birth for the same subject are recorded with minor variation, for example the adoption of a nickname or abbreviated name over time, or the incorrect recollection of a date of birth

A study attempting to investigate more subtle indicators of morbidity compared sub-clinical outcomes in 226 male migrants to a desert country who were established farm workers with 226 referents and 92 new migrant farm workers (Gomes, Lloyd et al. 1998). Acetyl cholinesterase activity was measured in subjects, who were also examined for aiming and digit symbol tests. A morbidity profile was collected by questionnaire. Established farm workers showed significantly reduced erythrocyte acetyl cholinesterase activity and significantly lower aiming and digit symbol tests. Irritated conjunctiva (47.3%), watery eyes (52.2%), blurred vision (63.3%), dizziness (55.2%), headache (63.7%), muscular pain (61.1%), and weakness (76.6%) were also reported significantly more commonly by established farm workers. Sub clinical symptoms such as these cannot be investigated in studies relying on disease or death registration as a measure of outcome. However, since results from the morbidity survey rely on self-reported outcome, they are open to reporting bias.

2.4.4 Market Gardeners and Orchardists

A Danish study followed a cohort of 4,015 employed gardeners (859 females and 3,156 males) from May 1975 until the end of 1984 with regard to cancer incidence (Hansen, Hasle et al. 1992). The observed cancer incidence was compared with expected numbers calculated from national incidence rates. For all cancer sites combined, the standardized morbidity ratio (SMbR) was 104. Among male gardeners a significantly increased incidence was seen for soft tissue sarcoma (SMbR = 526, 95% confidence interval (CI): 109-1,538), and chronic lymphatic leukaemia (SMbR = 275, 95% CI: 101-599). The incidence of non-Hodgkin's lymphoma was twice that which was expected SMbR 200, 95% CI: 86-393).

In a similar cohort, 2370 subjects who had been members of a Swedish horticulturists' trade association (market gardeners and orchardists) during the period 1965-1982 were compared to a regional reference population (Littorin, Attewell et al. 1993). Total mortality (542 deaths;

SMR , 0.8; 95% CI, 0.7-0.9) and mortality due to malignant tumours (133 deaths, SMR , 0.9; 95% CI, 0.7-1.0), and cardiovascular and respiratory deaths were somewhat decreased. Suggestive excesses in mortality were seen for mental disorders and tumours of the stomach, skin and nervous system. Tumours of the nervous system were in particular excess in the young and middle-aged horticulturists (below age 60; six cases, SMR 2.9; 95% CI 1.1-6.2).

When subjects were matched with the National Swedish Tumour Registry for the period 1965-1986, the total incidence of cancers was slightly decreased (255 cases; SIR, 0.9; 95%CI 0.8-1.0), as were gastrointestinal and respiratory tract tumours. The incidence of melanomas was increased (15 cases, SR = 2.1; 95% CI 1.2-3.5), and brain tumours in the young and middle-aged horticulturists (11 cases, SMR = 3.2; 95%CI 1.6, 5.7), including meningiomas (four observed, SMR = 6.8; 95%CI 1.9, 17.4), were increased, especially in the period 1975-1979.

2.4.5 Grain Millers

Grain millers can be potentially exposed to pesticides either through contact with treated grain, or through their involvement in the application of pesticides to stored grain. They can, however, also face potentially confounding occupational exposures such as mycotoxins.

One study followed a cohort of 22,938 white males who were enrolled in the life insurance program of the American Federation of Grain Millers during the period 1955 through 1985 (Alavanja, Blair et al. 1990). All facilities involved in the study were asked for details of pesticide use. Exposure to pesticides for various work groups was estimated from interviews with cohort members, site managers and hygienists and site inspection of 10 plants. Where job title was not available (75% of all deceased subjects) subjects were given an average exposure for that plant. SMRs were calculated on the basis of 5-year mortality rates among the U.S. white male population. Significantly fewer deaths were observed among the cohort than expected for all causes of death combined (SMR 89). Non-significant excess risks for developing non-Hodgkin's lymphoma (NHL) (SMR = 149), leukemia (SMR = 136), and pancreatic cancer (SMR = 133) were restricted to workers employed in flour mills, where pesticides are used more frequently than in other segments of the industry. SMRs for these

cancers were considerably less than 100 in other industry subdivisions. A nested case-control analysis was undertaken comparing the deaths from these cancers in different groups. Excess risks were observed for flour mill workers for NHL (odds ratio (OR) = 4.2}, pancreatic cancer (OR = 2.2) and leukemia (OR = 1.8). For both non-Hodgkin's lymphoma and pancreatic cancer, the risk increased by time lapsed since first employment. Within the flourmills, the workers who had ever worked in the maintenance department (OR = 8.1) or in the elevator department (OR = 2.8) were at particularly elevated risk of developing NHL.

748 deaths among active and retired corn wet-milling workers between 1947 and 1981 were identified from company and trade union records and underlying cause of death was determined from death certificates(Thomas, Krekel et al. 1985). Cause-specific Proportionate Mortality Ratios (PMR's) were computed for white and black males using US males as a comparison with adjustments for age, race, and calendar year of death. There were deficits of deaths from respiratory and digestive diseases. Among whites, mortality from chronic nephritis, bladder cancer, and lymphatic and haematopoietic malignancies was elevated. There was an elevated frequency of deaths due to diabetes and a threefold excess of pancreatic cancer deaths among blacks. Crude work history information indicated a small cluster of pancreatic cancer deaths among whites and blacks who had worked in production processes that convert cornstarch to syrup and dextrins. An elevated frequency of deaths from leukaemia was seen among white maintenance workers. The PMR methodology suffers from the limitations of "healthy worker effect" and is also dependant on the accurate recording of all deaths to prevent underestimation. The adequacy of records in this study is not discussed. Work categories and possible occupational exposures of subjects in this study are also broad.

In summary, most cohort studies have been limited by the impact of the healthy worker effect, comparisons with the general population and limited exposure information. Several outcomes have been identified in more than one study and are worthy of further investigation. These include leukaemia, lymphoma, brain cancer, prostate cancer, pancreatic cancer (in grain millers), and diabetes.

2.5 CASE-CONTROL STUDIES

By restricting the analysis to a specific disease of interest, case-control studies allow resources to be directed to better estimating the factors potentially influencing that outcome. Case-control studies examining the health impact of pesticides are often "nested" within the framework of an occupational cohort. Many of the flaws of cohort studies in relation to the evaluation of pesticides are also valid for case-control studies. Compared to cohort studies however, case-control studies are also open to bias in the selection of both cases and controls, and in subject recall. On the other hand, judicious selection of controls may overcome issues arising from the healthy worker effect and reference group limitations inherent in registry based cohort studies.

2.5.1 Suicide

A Canadian case-control study investigated an hypothesis linking pesticide exposure to increased rates of suicide in farm operators (Pickett, King et al. 1998). The study was nested in the Canadian Farm Operator Cohort, defined by the linking of Agricultural and Population censuses, farm register and mortality records. 1,457 male farm operators who committed suicide between 1971and 1987 were compared with a frequency matched (by age and province) sample of 11,656 control farm operators who were alive at the time of death of individual cases. Comparisons focused on past exposures to pesticides reported to the 1971 Canada Census of Agriculture. After controlling for important covariates, multivariate logistic regression analyses indicated no associations between suicide and acres sprayed with herbicides, acres sprayed with insecticides, or with the costs of agricultural chemicals purchased. There was, however, a suggestive increase in risk for suicide associated with herbicide and insecticide spraying among a subgroup of farm operators who were most likely to be directly exposed to pesticides: OR 1.71 (95% CI, 1.08-2.71) for 1-48 compared with 0 acres sprayed. The study concluded that the results did not provide strong support for the hypothesis that exposure to pesticides is an important risk factor for suicide among farmers. As with most ecological studies, exposure misclassification could explain these null findings. In particular, pesticide use may only impact on suicidality during active use, which may not be adequately identified by exposure classification using past Census records.

2.5.2 Colorectal cancer

A number of case reports and ecological studies have suggested an association between pesticide exposure and colorectal cancer (Forastiere, Quercia et al. 1993). At least one cohort study has also found an association between rectal cancer and pesticide users (Zhong and Rafnsson 1996). One case-control study examined serum organochlorine levels among 31 Egyptian colorectal patients and 17 controls who were healthy friends of other cancer patients (Soliman, Smith et al. 1997). Controls were deliberately chosen from different but similar geographic areas than cases to avoid sampling controls who had been exposed to the same dose of pesticides in the same locale as cases. This appears to introduce the possibility of significant selection bias into the study. High levels and large inter-individual variability of organochlorine levels were found among most subjects, especially those from rural areas. Farming and aging were each associated positively with high serum organochlorines. While the paper reports colorectal cancer patients having higher serum organochlorines levels than controls, this was not significant. In addition, the presence of cancer may have altered the body state of cases who were on average lighter than controls. This may in turn have had an influence on organochlorine storage and blood levels.

2.5.3 Breast cancer

Perhaps the most intensively investigated cancer in recent years in relation to pesticides is breast cancer. Case studies and small analytical studies undertaken in the early 1990s suggested an association between breast cancer and organochlorine pesticides, in particular DDT (Falck, Ricci et al. 1992; Wolff and Toniolo 1995). It was thought this association was physiologically plausible since DDT is known to be persistent within the body and to have oestrogenic properties and so might act as a tumour promoter in hormonally sensitive cancers. More recent, large and well-designed studies have generally not supported this hypothesis.

This research is complicated by the possibility that where exposure to DDT is estimated from current levels of DDT or its metabolites in blood, these levels themselves may be influenced by disease inception. This issue was overcome by one large study that examined plasma levels of DDE and PCBs in 240 women who gave a blood sample in 1989 or 1990 and who

were subsequently given a diagnosis of breast cancer before June 1, 1992 (Hunter, Hankinson et al. 1997). These levels were compared with those measured in matched control women in whom breast cancer did not develop. Data on DDE were available for 236 pairs, and data on PCBs were available for 230 pairs. The median level of DDE was lower among case patients than among controls (4.71 vs. 5.35 parts per billion, P=0.14), as was the median level of PCBs (4.49 vs. 4.68 parts per billion, P=0.72). The multivariate relative risk of breast cancer for women in the highest quintile of exposure as compared with women in the lowest quintile was 0.72 for DDE (95 percent confidence interval, 0.37 to 1.40) and 0.66 for PCBs (95 percent confidence interval, 0.32 to 1.37). Exposure to high levels of both DDE and PCBs was associated with a non-significantly lower risk of breast cancer (relative risk for women in the highest quintiles of both DDE and PCBs as compared with women in the lowest, 0.43; 95 percent confidence interval, 0.13 to 1.44).

A similar nested study compared 150 breast cancer cases and 150 controls drawn (in 3 racial groupings) from a cohort of 57,040 women from the San Francisco Bay who had previously taken a multiphasic health examination, independent of concern about risk of breast cancer, in the late 1960s (Krieger, Wolff et al. 1994). At that time, a sample of blood was obtained, then frozen and stored. The cohort was followed-up until December 31, 1990. Matched analyses found no differences in the case patients' and control subjects' serum levels of DDE (mean difference, 0.2 ppb; 95% CI, -6.7-7.2). The results were not altered by adjusting for relevant confounders, including length of follow-up, year of diagnosis, or the case patient's menopausal and estrogen-receptor status. Organochlorine levels were significantly higher among black and Asian women compared with white women.

However, the most recent of these studies using stored blood in cohort nested case-control studies found a high serum concentration of p,p'-DDT to be associated with a more than three-fold significantly increased risk of cancer (Hoyer, Jorgensen et al. 2000). In this Danish study, 10,317 women between 25 and 80 years of age participating in a heart study donated blood twice, in 1976-1978 and again in 1981-1983. In a nested case-control study of 155 cases and 274 matched breast cancer free controls, mean organochlorine concentrations over the course of the two examinations was compared with cancer risk. For the group most exposed to p,p'-

DDT there was an odds ratio of 3.6 (95%CI 1.1-12.2). The authors argue that repeated assessment of exposure during a relevant time period might provide a more precise estimate than a single estimate. However, there was no significant association for the group with the greatest total DDT levels, nor for DDE, although for both substances odds ratios for these groups was greater than 1.0. In addition, total DDT levels at the two examinations correlated closely (correlation coefficient 0.81, $p<0.001$), suggesting spot testing for DDT and metabolites may give a reasonable measure of exposure over a more prolonged period. Subjects who lost weight had a concentration decline for total DDT that was significantly less than expected.

A multicentre study, without access to historical body samples, measured DDT in adipose tissue aspirated from the buttocks (van't Veer, Lobbezoo et al. 1997). Additional data on risk factors for breast cancer were obtained by standard questionnaires. 265 postmenopausal women with breast cancer but no evidence of metastasis (response rates 75-97%) were compared with 341 healthy controls matched for age and centre (response rates 22-91%). Women with breast cancer had adipose DDE concentrations 9.2% lower than control women, however levels were closer to controls where recruitment rates were higher. No increased risk of breast cancer was found at higher concentrations. The odds ratio of breast cancer, adjusted for age and centre, for the highest versus the lowest fourth of DDE distribution was 0.73 (95% confidence interval 0.44 to 1.21) and decreased to 0.48 (0.25 to 0.95; P for trend = 0.02) after adjustment for body mass index, age at first birth, and current alcohol drinking. Adjustment for other risk factors did not materially affect these estimates.

The possible association between organochlorines and breast cancer was also not supported by a summary analysis of occupational studies (Adami, Lipworth et al. 1995). This found a rate ratio for breast cancer in exposed compared with unexposed women of 0.84 (95 percent confidence interval (CI) = 0.50-1.33) for PCBs and 1.08 (CI = 0.68-1.58) for TCDD. Similarly, effect estimates close to unity were found in summary analysis of breast cancer case-control studies regarding levels of DDE and PCB in adipose tissue or serum.

A recent study of workplace exposures and male breast cancer examined 178 cases and 1041 controls drawn from the United States national mortality follow-back survey (Cocco, Figgs et al. 1998). No association with pesticide exposure was identified.

2.5.4 Cancer of the Brain

As discussed above, several ecological and cohort studies have suggested a possible link between pesticide exposure and brain cancer (Morrison, Semenciw et al. 1992; Viel, Challier et al. 1998) (Figa-Talamanca, Mearelli et al. 1993). A recent critical review concluded there was inadequate existing data to confirm an association between exposure to pesticides and the subsequent development of brain tumours in adults (Bohnen and Kurland 1995). As with other outcomes, the review reported that results of case-control studies are conflicting, in part because of biases in the selection of patients and controls, poor definition and ascertainment of the nature and extent of the exposure to pesticides, and a non-uniform approach to the collection of antecedent information. A number of the studies reviewed evaluated farmers as a group exposed to pesticides. However, since cancer incidence in farmers may reflect not only their possible exposure to pesticides, but also exposure to petrochemical products, exhaust fumes, mineral and organic dusts, and biological exposure to animals and microbes, the reviewers concluded it seemed more plausible that exposure to multiple agents and/or other factors, such as genetic predisposition, were most relevant with respect to brain tumour pathogenesis.

2.5.5 Cancer of the Pancreas

Pesticides have been associated with pancreatic cancer and deaths from diabetes in cohort studies in flour millers, although not generally among other cohort studies in farmers (Thomas, Krekel et al. 1985; Alavanja, Blair et al. 1990). A recent cohort study ((Cantor and Silberman 1999), see below under leukaemia) also identified increased mortality from pancreatic cancer when aerial pesticide applicators were compared to controls (RR 2.71; 95% CI 1.4-5.3), but not when compared to the U.S. population (SMR 140; 95% CI 88-212).

Several case-control studies have suggested an association between exposure to DDT and cancer of the pancreas, although one of these is severely flawed. Diabetes has also been

associated with organochlorine exposure in at least one study, and it has been suggested diabetes may be a risk factor for pancreatic cancer, although evidence for this is conflicting (Laws, Curley et al. 1967; Morgan, Lin et al. 1980; Manousos, Trichopoulos et al. 1981; Wong, Brocker et al. 1984; Calle, Murphy et al. 1998; Giovannucci, Rimm et al. 1998).

A large prospective study of lifestyle factors and pancreatic cancer followed 63,374 Norwegians over 12 years of follow-up from 1984/86 (Nilsen and Vatten 2000). 166 incident cases of pancreatic cancer were found in this study, which confirmed the influence of smoking and also identified a higher risk among men occupied in farming, agriculture or forestry (RR 2.1; 95% CI 1.1-4.0).

A study having some of the hallmarks and weaknesses of an ecological study evaluated cancer risks among farmers in central Italy (Forastiere, Quercia et al. 1993). Cancer cases (N = 1674, 17 sites) were selected from all deceased men aged 35-80 years; a random sample of 480 other decedents formed the control group. Personal data and residence history was obtained for all subjects from municipal records, and farmers were identified from membership of the local farmers pension fund. Pesticide use was categorised according to whether or not subjects had been licensed as a pesticide user. Farmers had a decreased risk of lung and bladder cancer and melanoma and non-significant excess risks for stomach, rectal, kidney, and non-melanoma skin cancer. Compared to non-farmers, stomach and kidney cancer were significantly increased among the farmers with > 10 years' experience, and stomach, rectal, and pancreatic cancer were increased among licensed pesticide users with > 10 years' experience. Only pancreatic cancer was significantly increased when comparison was to non-licensed farmers.

Sixty-six people with cytologically diagnosed pancreas cancer and one hundred and thirty-one controls were investigated in a case-control study of pancreas cancer in residents, aged 30-79 years, of 18 counties in south-eastern Michigan (Fryzek, Garabrant et al. 1997). Controls were frequency-matched to the cases on age, sex, ethnicity and county of residence by random-digit dialling. All study participants were administered a questionnaire to assess lifetime exposure to pesticides from both environmental and occupational sources, family history of cancer, past medical history, smoking history and demographic information. Only 30% of eligible controls

agreed to participate, interviewers were not blinded to subject category and past exposure was self-reported creating the potential for significant selection and reporting bias. A statistically significant increased risk was found for self-reported exposure to ethylan (a DDT analogue). Increased odds ratios were observed for self-reported exposures to chloropropylate and DDT, as well as for the summary group of organochlorine pesticides that included all of these materials, though these associations were not significant.

An earlier investigation related to a cohort mortality study among 5886 chemical manufacturing workers, which had been completed in 1987 and had shown increased mortality due to pancreatic cancer (Garabrant, Held et al. 1992). A nested case-control study of pancreas cancer was undertaken among these chemical manufacturing workers to identify risk factors for the disease. Twenty-eight verified cases of pancreatic cancer and 112 matched controls were studied. Next of kin of each subject were interviewed to determine lifestyle factors, including tobacco, alcohol, and coffee consumption. Written work records and interviews with co-workers were used to determine chemical exposures at the plant under study. DDT was associated with pancreatic cancer (risk ratio (RR) for ever exposed compared with never exposed = 4.8; 95% confidence interval = 1.3-17.6). Among subjects who had a mean exposure to DDT of 47 months, the risk was 7.4 times that among subjects with no exposure. Two DDT derivatives, Ethylan and DDD, were additionally associated with pancreatic cancer (RR = 5.0 and 4.3, respectively); exposures to these two chemicals were correlated, and it was not possible to determine whether each acted independently of the other. Smoking was identified as an independent risk factor, but controlling for smoking (and other potential confounders) in the analyses did not appreciably alter the risks seen for DDT, DDD, or Ethylan. The risk increased with both duration of exposure and latency since first exposure.

More recently, a large study of 484 cases of pancreas cancer and 2095 controls drawn from the general population used a job matrix to examine the influence of occupational exposure to pesticides (Ji, Silverman et al. 2001). Subjects were interviewed in person, and over 75% of controls invited to participate were interviewed. An increased risk of pancreatic cancer was found with identified occupational pesticide exposures as a whole (for moderate/high exposure

OR 1.4; (%% CI 1.0, 2.0). This relationship was strongest with fungicides and herbicides, and after adjusting for these there was no apparent risk for insecticides as a group.

Another case-control study of 108 cases of pancreatic cancer and 82 controls examined serum organochlorine levels at study enrolment (Hoppin, Tolbert et al. 2000). Median concentrations of DDE were significantly raised in cases after adjusting for lipid content (DDE 1290 versus 1030 ng/g lipid; p=0.05). However, there was no significant dose response relationship for DDE and the relationship diminished when PCBs were included in the analysis (OR 1.1; 95% CI 0.4-2.8). Findings in studies relying on serum concentrations of DDT in subjects presenting with cancer may be influenced by the effect of the disease on lipid storage.

One plausible explanation for a relationship between pesticide exposure and pancreatic cancer lies in modulation of oncogene expression. Pancreatic cancer has a high prevalence of K-*ras* mutations in codon 12. A recent study measured concentrations of organochlorine compounds in serum taken at diagnosis in 51 subjects with pancreatic cancer and compared them to 26 hospital recruited controls (Porta, Malats et al. 1999). Cases with K-*ras* mutations had significantly higher concentrations of DDT and DDE than cases with wild-type K-*ras* after adjusting for lipids (p= 0.02). Serum concentrations of DDT and DDE were also significantly higher in cases than controls, although concentrations in cases with wild-type K-*ras* were similar to controls.

2.5.6 Soft tissue sarcoma

A large number of studies have investigated a possible association between insecticide exposure and the relatively rare cancer, soft tissue sarcoma (STS). These followed early studies suggesting a relationship between STS and phenoxyacetic herbicides, which had been used by US military personnel in Vietnam in the defoliant “Agent Orange”. Several early studies also investigated whether STS may be related to other pesticides, in particular organochlorines, and chlorophenols (Hardell and Sandstrom 1979; Eriksson, Hardell et al. 1981; Woods, Polissar et al. 1987; Erikson, Hardell et al. 1990). While many of these were methodologically flawed, none demonstrated a statistically significant association. A cohort

study of 4015 Danish gardeners followed up for 10 years found a significant association with STS, but no exposure history was available (Hansen, Hasle et al. 1992).

Separate studies have investigated a possible association between STS and exposure to chlorophenols, chemicals largely used as wood preservatives, but also used in pesticide manufacture and including the pesticide pentachlorphenol. A recent population-based case control study of 295 pathologically confirmed cases and 1,908 controls (all male between 32 and 60) has suggested an association between chlorphenols and STS independent of phenoxyactic acid exposure (OR = 1.79, 95% CI 1.10-2.88) (Hoppin, Tolbert et al. 1998). Risk increased with duration of exposure. Exposure data was obtained from self reported occupational history shortly after diagnosis, introducing the potential for recall bias. However, this data was reviewed, and exposure estimated, by a blinded occupational hygienist. The validity of this approach is supported by the fact that none of the crude measures based on subjects' response were significantly associated with STS, while the exposure variable constructed by the hygienist was.

2.5.7 Multiple Myeloma

As described above, increased death rates from multiple myeloma (MM) have been reported in ecological and cohort studies (Viel and Richardson 1993) (Cantor and Blair 1984; Kristensen, Andersen et al. 1996).

A case-control study conducted in the province of Forli, Italy compared forty-six cases of MM (20 females, 26 males; mean age 64 years, range 40 to 74) identified through the local cancer registry in the years 1987-90, with 230 age and gender-matched controls from the general population (Nanni, Falcini et al. 1998). Subjects were interviewed in-person using a structured questionnaire focused on exposure to pesticides and other occupational and non-occupational variables. Recall bias is potentially a problem for this study since subjects were aware of their disease status. Significant associations were found for non-occupational factors such as education level, altitude of the place of residence, first-degree familiarity for haemato-lymphopoietic neoplasias and previous herpes zoster diagnosis. A non-significant increase in

MM risk was observed among workers in agriculture as a whole (odds ratio 1.31; 95%CI 0.62-2.74), while an increased risk was associated specifically with the cultivation of apples and pears (OR 1.75; 95% CI 1.05-2.91). Cases were also more likely to live in geographic areas likely to have higher pesticide use, although areas with less pesticide use were also more remote and diagnosis of MM less likely.

A nested cohort study within the American Cancer Society Cancer Prevention Study II examined 282 cases of multiple myeloma during the first 4 years of follow-up (Boffetta, Stellman et al. 1989). MM was associated with employment as a farmer (OR 2.7; 95% CI, 1.3-5.7) and with self-reported pesticide exposure. Since analysis included both incident and prevalent cases, these results may have been influenced by reporting bias.

2.5.8 Lung cancer

Excess cases of lung cancer associated with pesticide exposure have been reported in several cohort studies (Ditraglia, Brown et al. 1981; MacMahon, Monson et al. 1988). However, this is far from universal (Wicklund, Daling et al. 1988; Alberghini, Luberto et al. 1991; Cantor and Booze 1991). There is also weak evidence to suggest an association with exposure to DDT (Austin, Keil et al. 1989; Faustini, Forastiere et al. 1993). An early study of 1658 German agricultural workers with a follow-up period of up to 25 years identified a significantly raised SMR of 2.0 for lung cancer (Barthel 1981). Analysis was limited to a simple SMR calculation by 5-yr age group, loss to follow-up is not reported and selection bias was possible due to the inclusion in the cohort of workers identified by other subjects. One other difficulty in assessing such findings is accounting for differing smoking patterns between the cohort and the reference population. In this study the investigators questioned a random sample of 163 cohort members and compared their smoking history with an age and sex matched sample from the general population. There was no significant difference in smoking history.

A large multisite case-control study investigated the role of occupational exposures in the development of squamous-cell carcinoma of the lung in Uruguay (De Stefani, Kogevinas et al. 1996). All incident cases of cancer were identified in 5 major hospitals in Montevideo (response rate 97.4%). The responses of 270 lung cancer cases were compared with 383

controls with cancers at any other site, thus minimising the possibility for recall bias. Significant increases in risk were associated with workers in the construction industry, pipe fitters, bakers, and textile workers and those exposed to asbestos, silica dust, and DDT (OR 1.7; 95% CI 1.0-2.8). The relationship with DDT was dose dependent.

A case-control study in the US was nested in a larger cohort study that had previously reported increased mortality from lung cancer with increasing years licensed as a pest control worker in Florida (Blair, Grauman et al. 1983). An additional follow-up (1977-82) of this male cohort confirmed the excess (SMR 1.4; 95% CI 1.0-1.8) and the rising risk with increasing number of years licensed (SMR 2.2 among workers employed more than 20 years) (Pesatori, Sontag et al. 1994). The follow-up also showed a small excess for total cancers (SMR 1.2; 95% CI 1.0-1.4). There was little evidence of the healthy worker effect. The case-control study was undertaken to determine the effects of smoking and the type of pesticide exposure on lung cancer risk. Occupational histories and other data were obtained on 65 deceased lung cancer cases. Five controls were randomly matched to each case by age. Three controls were selected from those alive and two from deceased members of the cohort resulting in the selection of 122 deceased and 172 living controls. Interviews were conducted with next-of-kin regardless of the vital status of the subject with response rates of 83% for cases and 75-80% for controls. Bias has been minimised in this study by using deceased controls to limit recall bias and from high and similar response rates between groups. Using information from licensing records, ORs for lung cancer were greater for workers first licensed before age 40 (OR 2.4; 95 %CI,1.0-5.9 with deceased controls) and increased from 1.4 (95%CI, 0.7-3.0) for subjects licensed 10-19 years to 2.1 (95%CI,0.8-5.5) for subjects licensed 20 or more years. Using living controls, an association with duration of employment was observed when years of licensure were lagged five years, but was not observed in unlagged analyses.

It is worthy of note that, while tobacco use was strongly correlated with lung cancer in this study with only one case identified as a non-smoker, tobacco did not confound risk estimates. This has also been reported by other studies. Comparison of crude and smoking adjusted SMRs in a study of US veterans showed the two measures to be remarkably similar. The correlation coefficients between crude and smoking-adjusted SMRs were .88 for lung cancer,

.98 for bladder cancer, and .97 for colon cancer, indicating that the absence of information on smoking, even for studies of tobacco related cancer, seldom confounds risk estimates (Blair, Steenland et al. 1988). Nor does it appear that non-smokers seek out cleaner (and therefore less exposed) jobs than smokers (Siemiatycki, Waeholder et al. 1988). Internal analyses of "dose-response" in cohort studies are therefore also unlikely to be seriously confounded by smoking habit.

2.5.9 Leukaemia

Ecologic and cohort studies have suggested increased rates of leukaemia among farmers, but this association may relate to a bovine mediated virus (Blair and Thomas 1979; Viel and Richardson 1993; Kristensen, Andersen et al. 1996) (Pearce and Reif 1990). However, other studies in groups such as gardeners have also found a possible association (Hansen, Hasle et al. 1992). A population-based case-control study undertaken in Iowa and Minnesota compared 578 white men with leukaemia and 1245 controls (Brown, Blair et al. 1990). Living controls were selected by random digit dialing and from Medicare records, and deceased controls were selected from death certificates. Control response rates were 77-79%. Interviews were conducted with cases or close relatives. The study found slight, but significant, elevations in risk for all leukaemia (OR, 1.2) and chronic lymphocytic leukaemia (OR, 1.4) for farmers compared to non-farmers. These relationships did not appear to be related to duration of farming. There were no significant associations with leukaemia for exposure to specific fungicides, herbicides, or crop insecticides. However, significantly elevated risks for leukaemia of greater than or equal to 2.0 were seen for exposure to specific animal insecticides including the organophosphates, crotoxyphos (OR 11.1), dichlorvos (OR 2.0), famphur (OR 2.2), pyrethrins (OR 3.7) and the chlorinated hydrocarbon methoxychlor (OR 2.2). There were also smaller, but significant, risks associated with exposure to nicotine (OR 1.6) and DDT (OR 1.3). The risk tended to be greater with use of insecticides on animals and with time since first use.

However, a death certificate based case control study of 1499 cases of leukaemia and 1499 controls matched from other deaths failed to find a significant association with farming or insecticide exposure estimated by characteristics of county of origin (Blair and White 1981). A number of flaws potentially biasing this study to the null have been discussed above.

A case-control study of chronic lymphatic leukaemia was also undertaken in Sweden among 111 patients from five hospitals diagnosed between 1964 and 1984 and surviving until 1981 and 431 controls living in the same catchments (Flodin, Frederiksson et al. 1988). Exposure information was obtained by questionnaire posted to all subjects introducing the potential for recall bias. Multiple linear regression identified significant associations with age, engine exhausts, DDT and contact with horses.

A cohort mortality study was conducted of 9,677 male aerial pesticide applicators and 9,727 flight instructors identified from computerized US Federal Aviation Administration medical examination records from 1965-1979 (Cantor and Booze 1991). Vital status of subjects was determined through January 1, 1980, and standardized mortality ratios (SMRs) were calculated. Less than 2.5% of subjects were lost to follow-up. The overall SMR varied significantly between applicators (SMR 127; 699 deaths) and instructors (SMR 93; 454 deaths). Fatalities from non motor vehicle accidents, mostly aircraft crashes, were in notable excess, whereas deaths from most chronic diseases, including all cancer, were low (for total cancers there was no significant difference between the groups, applicators having an SMR of 74 and instructors SMR 64). The ability of the study to assess cancer risk among applicators was limited by a relatively brief follow-up period. However, applicators were significantly more likely to have died from leukaemia (SMR 171; 8deaths) than flight instructors (SMR 24;1 death). A number of factors argue against this being a true relationship. The seven deaths from leukaemia did not appear to be related to either number of hours flown (as a measure of exposure) or years since subject entry, and there was a diversity of leukaemia cell types. Over 20 individual cancers were compared between the groups and by chance one association would be expected.

This study was later extended to cover the period 1965-1988 (Cantor and Silberman 1999). The increase in mortality from leukaemia among pesticide applicators when compared to controls persisted when this longer period of follow-up was examined (RR 3.35; 95% CI 1.3-8.5). Applicators also had increased mortality from pancreatic cancer (RR 2.71; 1.4-5.3), total cancers (RR 1.18; 95% CI 1.01-1.37) and accidents when compared to controls. However,

when mortality in applicators was compared to the white U.S. population only accident mortality remained significantly elevated and the mortality ratio for leukaemia approached unity (SMR 118; 95% CI 64-198). There was also no trend for increasing leukaemia with increasing duration of exposure. This discrepancy may reflect the impact of the healthy worker effect, other differences between pilots and the U.S. population (who need to qualify medically to retain their licences), failure to identify all deaths, or a random reduction in mortality among the control population (SMR 34; 95% CI 9-86).

2.5.10 Prostate Cancer

Several ecological and cohort studies have suggested pesticide exposure may be linked to prostate cancer (Keller-Byrne, Khuder et al. 1997). One large recent cohort study identified a standardised incidence ratio of 1.13 (95%CI1.02-1.24) (Dich and Wiklund 1998). This study also undertook a literature review and identified 7 case control studies of prostate cancer where occupational analysis included farming or forestry. Only one showed a significantly elevated odds ratio.

2.5.11 Non Hodgkin's Lymphoma

A number of studies have examined a possible relationship between phenoxyacetic acid herbicides and non-Hodgkin's lymphoma (NHL). Some of these have also investigated possible associations with other pesticides. However, strong associations between usage of different pesticides make analysis of specific relationships difficult.

Persistent chemicals like the organochlorines allow estimates of past exposure. A recent case-control study examined organochlorine levels in serum taken in 1974 in 74 members of a prospective cohort of 25,802 members of the general community who had developed NHL and 147 matched controls (Rothman, Cantor et al. 1997). There was a strong dose response relationship with PCB concentrations. While DDT levels were higher in cases, this was not statistically significant, and the risk of NHL increased only weakly and non-significantly with increasing DDT concentrations. This relationship was further weakened when DDT levels were adjusted for PCBs.

Most other studies do not have the luxury of physiological exposure estimation. One study investigating soft-tissue sarcoma and NHL interviewed 576 cases of NHL and 694 controls matched from random digit dialling and Health Case Financing Administration files (Woods, Polissar et al. 1987). Deceased controls were chosen from death certificates. 76% of selected controls and 91% of cases or their proxies were interviewed. Exposure assessment was by self-report of occupation followed by the assignment of "high", "medium", "low" or "no" exposure categorisation for specific pesticides. Corroboration of categorisation was attempted with co-workers, however recall bias is still possible with self-reporting from cases aware of their condition. Self-reported exposure to DDT was significantly associated with NHL (OR 1.8; 95% CI, 1.0-3.2). A reported association with chlordane was not significant (OR, 1.6; 95% CI, 0.7-3.8). These risk estimates were not substantially altered after adjusting for other exposures.

In one case-control study, 60 cases of Hodgkin's disease and 109 cases NHL were combined and compared with 338 controls chosen from national population and deaths registries (Hardell, Eriksson et al. 1981). The study was stimulated by findings in 17 cases of histiocytic lymphoma of which 11 reported exposure to chlorophenols or phenoxy acids. These subjects appear to have been included as cases, potentially introducing some selection bias. Exposure was estimated by self-administered questionnaire also allowing reporting bias to influence findings. Exposure to herbicides or chlorphenols was significantly associated with cases (RR 6.0; 95% CI, 3.7-9.7). 13% of cases and 7.8% of controls reported exposure to DDT (odds ratio, 1.8; 95% CI, 1.0-3.2). This relationship was maintained but lost statistical significance when only subjects not reporting exposure to herbicides were considered (OR, 1.6; 95%CI, 0.6-4.1).

Most studies investigating the possible relationship between NHL and agricultural pesticide use have been in men. One recent population-based, case-control study conducted in eastern Nebraska, examined the risk of NHL lymphoma in women who had ever lived or worked on a farm (Zahm, Weisenburger et al. 1993). Cases were identified from the Nebraska Lymphoma Study Group and controls were selected from residents of the same area by frequency matching by race, sex, vital status and age. Telephone interviews were conducted with similar

high response rates for cases and controls. Subjects were not blind to the disease status. No overall relationship was identified for having worked on a farm (OR 1.0), however, the number of women who mixed or applied pesticides was small, particularly in comparison to men on farms. Small non-significant associations were observed among the women who personally handled insecticides (OR = 1.3) or herbicides (OR = 1.2). Women who personally handled organophosphate insecticides had a significant 4.5-fold increased risk NHL. Use of chlorinated hydrocarbon insecticides was associated with an OR of 1.6; however, the use on dairy cattle was associated with a 3-fold increased risk.

A case-control study of 201 cases of non-Hodgkin's lymphoma and 725 controls drawn from the general population using telephone interview to gather information on agricultural chemical exposure found no evidence for a link between NHL and farmers in general, or with overall use of insecticides (OR, 1.1; 95% CI, 0.7-1.6) (Zahm, Weisenburger et al. 1990). There was a 50% excess of NHL among men who mixed or applied 2,4-D (odds ratio (OR) = 1.5; 95% confidence interval = 0.9, 2.5), the risk increasing with the average frequency of use. Use of organophosphates was also associated independently with NHL and with 2,4-D use. These findings could be influenced by recall bias between cases with cancer and healthy controls.

Pooled data from three case-control studies from four mid-western states in the United States yielded 993 cases of NHL and 2918 controls (Baris, Zahm et al. 1998). Information on use of agricultural pesticides and other risk factors was gathered by telephone interviews. Response rates varied between cases and controls (91-96% and 78-94% respectively) and subjects were not blind to their disease status. Self-reported use of DDT was significantly associated with NHL (OR 1.2; 95% CI, 1.0-1.6), however adjustment for age, respondent status, state of residence, and use of other pesticides generally reduced ORs to near unity. The authors concluded that the excess risk initially found for DDT might be due to the use of other pesticides.

One physiological hypothesis that may explain a causative relationship between a number of pesticides and NHL relates to immunosuppression (Vineis, D'Amore et al. 1992). It is believed

that NHL is caused by common viruses, such as the Epstein-Barr virus, that induce proliferation and immortalization of B-cells, followed by T-cell impairment entailing cell-mediated immunodeficiency. TCDD (which is a contaminant of phenoxy herbicides), DDT, and chlorinated solvents have all been reported to induce impairment or suppression of cell-mediated immunity.

2.5.12 Cancer in offspring

Studies investigating a possible influence of pesticide exposure in parents on cancer incidence in their offspring have generally relied on parents recorded occupation on cancer and deaths registry notifications. Such records focus on current occupation and give little information on past work history. Results of the small number of studies undertaken in this area are inconsistent, but kidney cancer (Wilms' tumour), brain tumours, Ewing's bone sarcoma and acute leukaemia have all been associated with paternal pesticide exposure (Fear, Roman et al. 1998).

A recent review of epidemiologic studies published between 1970 and 1996 examined the possible association between pesticides and the risk of childhood cancers (Daniels, Olshan et al. 1997). The review found thirty-one relevant studies. In general, the reported relative risk estimates were modest and appeared to be stronger when pesticide exposure was measured in more detail. Frequent occupational exposure to pesticides or home pesticide use was more strongly associated with both childhood leukemia and brain cancer than either professional exterminations or the use of garden pesticides. Occupational pesticide exposure has also been associated with increased risk of Wilms' tumor, Ewing's sarcoma, and germ cell tumors. Residence on a farm, as a proxy for pesticide exposure, was associated with increased risk of a number of childhood cancers. The review concluded that, although increased risk of some childhood cancers in association with pesticide exposure is suggested by multiple studies, methodological limitations common to many studies restrict conclusions; these included indirect exposure classification, small sample size, and potential biases in control selection.

In one study, records for 167,703 childhood deaths occurring during 1959-63, 1970-78 and 1979-90 in England and Wales were analysed (Fear, Roman et al. 1998). Among the offspring

of men identified as having potential occupational exposure to pesticides there were 5270 deaths, of which 449 were due to cancer. Associations were assessed using proportional mortality ratios (PMRs), with adjustment for age, year of death and paternal social class. The only statistically significant excess was for kidney cancer (PMR=1.59, 95% CI=1.18-2.15, based on 42 deaths). The study concluded that, although these results offered some support for the suggestion that paternal occupational exposure to pesticides may be related to the subsequent development of kidney cancer in offspring, other explanations cannot be excluded.

Another large study examined incident cancer in offspring born between 1952 and 1991 to parents identified as farm holders in agricultural censuses in Norway in 1969-1989 (Kristensen, Andersen et al. 1996). The study used a range of different exposure indicators based on census information. In the follow-up of 323,292 offspring for 5.7 million person-years, 1,275 incident cancers were identified in the Cancer Registry for 1965-1991. The study found a standardized incidence for all cancers equal to the total rural population of Norway, but cohort subjects had an excess incidence of nervous-system tumours and testicular cancers in certain regions and strata of time that could imply that specific risk factors were of importance. The biggest overall risk factor for brain tumours was pig farming (rate ratio (RR), 3.11; 95% CI, 1.89-5.13). Indicators of pesticide use had an independent effect of similar magnitude in a dose-response fashion, strongest in children aged 0 to 14 years (RR, 3.37; 95% CI, 1.63-6.94). Horticulture and pesticide indicators were associated with all cancers at ages 0 to 4 years, Wilms' tumour, non-Hodgkin's lymphoma, eye cancer and neuroblastoma. Chicken farming was associated with some common cancers of adolescence, and was strongest for osteosarcoma and mixed cellular type of Hodgkin's disease. This large study was weakened by the crude exposure indicators available and comparison between farm holders and the general population. Both are likely to bias any true association towards unity. Identified associations might also result from a range of confounding factors.

2.5.13 Endocrine and Reproductive Disorders

Reproductive disorders in birds were among the first adverse impacts linked to pesticide exposure. Many of these disorders are believed to be mediated through hormonal disruption. More recently, a number of other endocrine disorders have been identified in ecological

communities near contaminated sites or in laboratory studies. These include sex differentiation, and masculinisation or feminisation in wild populations of fish, alligators and birds, and thyroid hormone disruption (Fry 1995; Safe 1995; Kelce and Wilson 1997; de Solla, Bishop et al. 1998).

Epidemiological trends since the 1940's, including increasing rates of breast and testicular cancer and falling sperm counts in men (Carlsen, Giwercman et al. 1992; Sharpe and Skakkebaek 1993), have also prompted suggestions that environmental exposures may be causing endocrine disruption in human populations. A number of pesticides have been demonstrated to act as hormonal agonists or antagonists in *in vitro* tests for hormonal activity. These include DDT and metabolites (oestrogenic activity) (Chen, Hurd et al. 1997), DDE (anti-androgen activity)(Kelce, Stone et al. 1995), organophosphates**,** and pyrethroids (Garey and Wolff 1998). This has lead to concerns that environmental pesticide exposure may be causing adverse heath effects in the general community through endocrine disruption. These concerns were supported by early research suggesting high levels of organochlorines in maternal and foetal blood were associated with miscarriage and premature labour (O'Leary, Davies et al. ; Saxena, Siddiqui et al. 1980).

However, the dietary oestrogenic contribution of all industrial chemicals has been estimated at only 0.0000025% that of bioflavinoids, which are naturally widespread in the human diet (Safe 1995). In addition, a recent reanalysis of the data showing a decrease in male sperm counts of over 40% during the period 1940 to 1990 has questioned the adequacy of statistical methods used in this assessment(Bromwich, Cohen et al. 1994). The reanalysis concluded that the data did not support a significant decline in sperm count. Evidence from epidemiological studies of possible endocrine outcomes in humans is limited and conflicting.

One study supporting the hypothesis that pesticide exposure may influence sperm production was undertaken in a large Chinese pesticides factory (Padungtod, Lasley et al. 1998). Thirty-four randomly selected workers exposed to organophosphates were compared with 44 unexposed workers from a nearby textile factory. A quantitative pesticide exposure assessment was performed among a subset of the exposed and unexposed workers, and information on

potential confounders was collected in an interview. A single blood sample was collected at the end of a work shift, when each subject also donated a semen sample. Three first-voided urine samples were also collected from each worker on 3 consecutive days. Urinary p-nitrophenol level at 1 hour after the work shift correlated with serum ($r = 0.71$, $P < 0.01$) and urinary ($r = 0.51$, $P = 0.04$) FSH levels. Stratifying by the subjects' exposure status, the investigators found a significant negative correlation among the exposed group between urinary FSH level and sperm count ($r = -0.61$, $P < 0.01$) and between urinary FSH level and sperm concentration ($r = -0.53$, $P = 0.03$). Pesticide exposure alone was significantly associated with serum LH level (beta (coefficient of exposure effect) = 0.79; 95% confidence interval (CI) = 0.42, 1.16) but not with serum FSH or testosterone or with any urinary hormone levels. With adjustment for age, rotating shift work, current cigarette smoking, and current alcohol consumption, exposure significantly increased the serum LH level by 1.1 mIU/mL (95% CI = 0.34-1.82). Meanwhile, the serum FSH level was slightly elevated (beta (coefficient of exposure effect) = 1.38; 95% CL = -0.09, 2.85) and the serum testosterone level was decreased (beta = -55.13; 95% CL = -147.24, 37) with increased pesticide exposure. The authors concluded that organophosphate pesticides have a small effect on male reproductive hormones.

A study of anglers possibly exposed to fish from the Great Lakes region contaminated with halogenated organics, heavy metals, and pesticides did not support the hypothesis that this exposure influenced “time to pregnancy”(Buck, Sever et al. 1997). Structured telephone interviews were conducted with 2,445 of 2,977 (82%) female cohort members (anglers and their spouses) aged 18-40 years who had stated on enrolment they were considering pregnancy. 42% reported eating contaminated fish from Lake Ontario despite health advisories. Among the 1,234 women who reported being pregnant, 874 (71%) had a known TTP and comprised the study sample. When multiple regression models were developed including number of years of fish consumption (duration) and other covariates, fish consumption and maternal age accounted for virtually none (0.5%) of the explained variance.

On the other hand, a study from the Netherlands of 91 children to 43 fruit growing couples during the period 1978-1990 did find an association between exposure and time to pregnancy

(de Cock, Westveer et al. 1994). The study population consisted of 447 fruit growers out of around 3000 members of a grower's organisation who had participated in a research program on pesticide exposure and were willing to participate in follow-up studies. Information on time taken to conceive was gathered by face-to-face interview. Recruitment and recall biases could therefore explain some study findings. Time to pregnancy was examined after correction for gravidity and consultation with a physician for fertility problems. Self reported application of pesticides was associated with a long time to pregnancy, resulting in a fecundability ratio of 0.46 (95% confidence interval (95% CI 0.28-0.77). The effect of exposure was mainly apparent if the couple had intended to become pregnant in the period from March-November (fecundability ratio 0.42, 95% CI 0.20-0.92). This was the period in which pesticides are applied. Out of the spraying season the effect of a high exposure was absent (fecundability ratio 0.82, 95% CI 0.33-2.02). In the high exposure group 28% of the pregnancies had been preceded by consulting a physician because of fertility problems, compared with 8% in the low exposure group.

Another outcome later investigated in these subjects was the ratio of male to female births (James 1995). While the overall sex ratio was not different from the expected ratio, a decrease in sex ratio was found when recent years of birth were compared with earlier pregnancies. Such a finding is less likely to be explained by recall bias.

A number of studies have examined the possible influence of pesticide exposure on pregnancy outcome (O'Leary, Davies et al. 1970). One recent review concluded that many of the epidemiologic studies to date suffered from methodologic problems. Nevertheless, the authors considered the data to be suggestive of increased risks of fetal deaths associated with pesticides in general and maternal employment in the agricultural industry (Arbuckle and Sever 1998). A separate review found the evidence inconclusive.(Nurminen 1995)

Another review concluding there was increasing evidence for reproductive and developmental effects of both maternal and paternal pesticide exposure expanded on the methodological problems plaguing these studies:

> "Case-control studies of individual types of malformations are often limited by small sample size and the relative infrequency of specific exposure. Cohort studies are limited by the low prevalence at birth of even the most common malformations. Complicating both case-control and cohort studies are major issues related to the accuracy and specificity of assessment/classification of exposure, let alone dose; classification and grouping of malformations; and multiple comparisons."(Sever, Arbuckle et al. 1997)

As discussed above, this review examined studies of the possible effects of dioxin-contaminated Agent Orange used by military personnel during the Vietnam war to demonstrate these problems.

Two themes were of particular note. A large multifaceted study mandated by the US Congress interviewed a random sample of male veterans by telephone (Study 1988). Over 1500 exposed and non-exposed personnel were interviewed with response rates of 84% for each group, with Vietnam veterans reporting 40-50% more birth defects than non Vietnam veterans. This led to a sub-study to examine birth defect rates as identified by hospital records. This found that agreement between veterans reports and hospital records for birth defects was relatively poor (and generally under-reported) for both cohorts, but more so for Vietnam veterans. No association between Vietnam duty and outcome was found when objective outcome criteria were used.

The second key methodological issue related to exposure assessment. As described in more detail above, when results of individual serum TCDD (the dioxin contaminant of Agent Orange) became available to verify presumed exposure patterns, these levels correlated poorly with self reported exposure and exposure indices developed from military records.

These issues are reinforced by a study in Columbia that examined the prevalence of adverse reproductive outcomes in a population of 2951 men and 5916 women who had been working in the floriculture industry (Restrepo, Munoz et al. 1990). The prevalence rates for abortion, prematurity, stillbirths, and malformations were estimated by interviewer administered

questionnaire for pregnancies occurring among the female workers and the wives of the male workers before and after they started working in floriculture. These rates were also related to various estimated degrees of exposure. A significant increase in the prevalence of abortion, prematurity, and congenital malformations was detected for pregnancies occurring after the start of work in floriculture. However, for abortion and for husband-reported prematurity, the risk disappeared for pregnancies occurring most recently suggesting the association might be due to recall bias as subjects tend to have less recall of events that occurred in the distant past. Overall rates for spontaneous abortion in the study were also low suggesting severe underreporting. This was worse when the history was given by the woman's husband. When a nested case-control study for congenital malformations was undertaken, 53% of the children reported as malformed by their parents were in fact normal, and 8% of those reported as normal were malformed.

A case-control study of birth defects nested in this same survey investigated a total of 535 children born to these workers and reported by their parents as malformed, and 1070 "normal" children selected at random from the cohort as controls(Restrepo, Munoz et al. 1990). Subjects were examined and their medical records reviewed. Seventy-six percent of both groups attended the examination. The problem of misclassification in self-reported outcome assessment is emphasised by birth defects being confirmed for only 154 (38%) of 403 children reported as malformed. 68 of 817 children reported as normal were found to have a birth defect. A case-control analysis was then carried out including 222 children with birth defects and 443 referents. An increased risk was found only for birthmarks, and specifically for haemangiomas, for children with parents exposed to pesticides in the floriculture industry.

A hospital-based case-control study investigated stillbirths in a central Texas community that included a facility with a more than 60-year history of producing primarily arsenic-based agricultural products(Ihrig, Shalat et al. 1998). 119 cases were compared with 267 controls randomly selected from healthy live-births at the same hospital and matched for year of birth. The authors examined medical and demographic data for the period January 1, 1983, to December 31, 1993, and estimated socioeconomic status by median income from the 1990 Population and Housing Census data. Arsenic exposure levels were estimated from airborne

emissions and an atmospheric dispersion model linked to a geographical information system (GIS) database. Exposure was linked by GIS to residential address at time of delivery. A conditional logistic regression model was fitted including maternal age, race/ethnicity, parity, income group, exposure as a categorical variable, and exposure-race/ethnicity interaction. The prevalence odds ratio observed for subjects with high exposure was significantly elevated (POR 4; 95% CI, 1.2-13.7), however this association was limited to Hispanic subjects (POR, 8.4; 95% CI, 1.4-50.1) suggesting the finding may have been influenced by other factors.

Another study investigating reproductive outcomes was undertaken in central Sudan (Taha and Gray 1993). 197 stillbirths recorded in a local hospital and 36 perinatal deaths identified in the local community; were compared with 812 live born, normal-birth-weight infants in the hospital, and 1505 live born infants who survived for the first 7 days after birth in the community. The odds ratio (OR) of perinatal death associated with pesticide exposure estimated by multiple logistic regression was elevated in both the hospital (adjusted OR 1.9; 95% CI: 1.3-2.8) and the community populations (adjusted OR 2.7; 95% CI: 1.1-6.4). The OR was significantly higher among women engaged in farming (3.6; 95% CI: 1.6-8.0), but not among women in non-farming occupations (1.6; 95% CI: 0.8-3.3). The estimated attributable risks of perinatal death owing to pesticide exposure were 22.6% for hospital stillbirths and 15.7% for community perinatal deaths.

A series of studies undertaken in New Brunswick, Canada, could not provide clear evidence for an association between pesticide exposure and reproductive problems.(White, Cohen et al. 1988) Geographic and temporal analyses, and case-control studies using vital statistics, hospital records, the Canadian Congenital Anomalies Surveillance System and chemical databases, revealed no association with pesticides used in forestry. Exposure was estimated from aerial spraying records of the New Brunswick Department of the Environment and soil capability maps. Evidence of an association between the potential exposure to agricultural chemicals and three major anomalies combined as well as spina bifida without hydrocephalus was found, although this was not considered physiologically plausible. An observed association between stillbirths and such exposure during the second trimester of pregnancy was consistent with cyclic patterns of still birth in the area.

An early study in New Zealand, compared the reproductive history of 548 professional 2, 4, 5-T sprayers and 441 agricultural contractors who were sent a questionnaire (89% and 83% response rates respectively) examining births, congenital defects, and miscarriages between 1969 and 1980 (Smith, Fisher et al. 1982). Each pregnancy outcome was classified according to whether or not the father sprayed 2,4,5-T during the year of the pregnancy outcome, or the previous year. The relative risk estimates of 1.19 for congenital defects, and 0.89 for miscarriages, were not statistically significant. However, the numbers of birth defects (total 26) were inadequate to examine specific conditions, and both heart defects and the single case of anencephaly were all in the exposed group.

Farm Couples identified in Ontario from the 1986 Canadian Census of Agriculture, were given a questionnaire concerning farm activities, reproductive health experience, and chemical applications (Savitz, Arbuckle et al. 1997). Male farm activities in the period from 3 months before conception through the month of conception were evaluated in relation to miscarriage, preterm delivery, and small-for-gestational-age births. Among the 1,898 couples with complete data (64% response rate), 3,984 eligible pregnancies were identified. Self-reported miscarriage was not associated with chemical activities overall but was increased in combination with reported use of thiocarbamates, carbaryl, and unclassified pesticides on the farm. Preterm delivery was also not strongly associated with farm chemical activities overall, except for mixing or applying yard herbicides (OR, 2.1, 95% confidence interval 1.0-4.4. No associations were found between farm chemicals and small-for-gestational-age births or altered sex ratio. This study is weakened by the subjective exposure and outcome assessment.

An Indian study compared the reproductive histories of 1016 couples in which the males were employed mixing and spraying pesticides including organochlorines, organophosphates and pyrethroids, with 1020 couples who were not exposed to pesticides but belonged to the same socioeconomic group and age range (Rupa, Reddy et al. 1991). Outcome was self reported and analysis was limited to univariate chi-squared testing, although the couples were stratified by male smoking status. Exposed males reported a significant decrease in fertility and a significant increase in abortions among their wives compared to the control group. The

frequency of live births decreased significantly, and still births, neonatal deaths, and congenital defects showed a significant increase in the offspring of exposed males. Smokers exposed to pesticides showed a higher effect than nonsmokers exposed to pesticides. The percentage of births with malformations was 3.02% among exposed subjects and 0.7% in unexposed subjects. Since the latter figure is well below the 2-3% of newborns usually expected to have defects, reporting bias may have been a significant problem with this study.

A recent case control study compared 86 women with endometriosis and 70 controls undergoing laparospcopy for chronic pelvic pain (Lebel, Dodin et al. 1998). There was no significant differenced in mean organochlorine plasma concentrations of 14 polychlorinated biphenyl congeners and 11 chlorinated pesticides between the cases and controls. There was also no significant linear trend in the adjusted odds ratios for endometriosis as organochlorine concentrations increased.

Another possible outcome of endocrine disruption might be bone mineral density, which is regulated by the antagonistic effect of androgens and oestrogens. A recent small study of 68 sedentary women with an adequate intake of calcium found an association between log DDE in serum and bone mineral density, after adjusting for age, and hormone replacement therapy(Beard, Marshall et al. 2000). However, the authors reinforce that these findings were in a small, cross sectional sample and need to be viewed with caution**.**

2.5.14 Neuropsychological effects

High exposures to pesticides in humans can have persistent neurologic effects, even in the absence of acute symptoms of intoxication or after their resolution (Keifer and Mahurin 1997). Effects have been reported in both the peripheral nervous system (sensory, motor and autonomic neuropathies) and the central nervous system (changes in cognition, personality and behaviour).

In addition to acute cholinergic poisoning, organophosphorus (OP) compounds are capable of producing several subacute, delayed and chronic neurological, neurobehavioural and psychiatric syndromes. These include a well defined “intermediate” syndrome,

organophosphate induced delayed neuropathy (OPIDN, mediated through inhibition of neuropathy target esterase) and a number of chronic neurological and psychiatric disorders (Abou-Donia 1981). OPIDN generally follows a clinically severe OP intoxication and becomes manifest after a delay period, first as sensory changes followed by foot drop and, in severe cases, paralysis. Lesions are characterized by degeneration of axons with subsequent secondary degeneration of myelin in both the peripheral and central nervous systems. Recovery is only likely in mild cases, whereas more severe cases show symptoms of an upper motor neuron lesion in the lower limbs. Research in animals suggests that concurrent exposure to more than one OPIDN inducing pesticide produces greater neurotoxicity than that caused by individual exposures (Abou-Donia, Wilmarth et al. 1996).

A number of epidemiological studies have suggested an association between chronic pesticide exposure, in particular organophosphate exposure, and adverse neuropsychological outcomes. Other studies have, however, failed to find an association (Daniell, Barnhart et al. 1992).

In a study of subclinical outcomes, 208 pesticide formulators, 172 pesticide applicators, and 223 control subjects chosen from the same communities as the exposed (72 from an urban region matching the formulators and 151 from a rural area matching the applicators) were assessed in the field by 2 psychiatrists (Amr, Halim et al. 1997). It is not reported whether the clinicians were blinded to the subjects' category. Subjects were assessed by applying a recognized system of diagnosis and classification in an open clinical interview. Subjects were also screened for psychiatric morbidity using a standardized screening tool, the General Health Questionnaire. Significantly higher frequencies of psychiatric disorders were found in the exposed groups using both the standardised and open assessments. The predominant diagnosis was depressive neurosis, while the most frequent symptoms were irritability and erectile dysfunction.

Male pesticide applicators licensed in the state of New York were interviewed and examined to investigate the effect of exposure to organophosphate pesticides on the peripheral nervous system (Stokes, Stark et al. 1995). Population based controls were identified through motor vehicle records, matched for age, sex and residence and recruited by post. 90 of a possible

554 applicators agreed to participate, and 68 of 450 potential controls. These low rates introduce the possibility of recruitment bias. Subjects were questioned off season (November 1988-February 1989) and again during the spraying season (April 1989-August 1989) about the presence of several acute signs and symptoms. Short term exposure was validated by measuring the concentration of dimethylthiophosphate (DMTP), a metabolite of guthion, in urine. Chronic signs of subtle peripheral nerve damage were determined by vibration threshold sensitivity of the farmers and applicators tested during November 1988-February 1989 and compared with controls drawn from the general population who were tested during the same time period the next year (November 1989-February 1990). Mean vibration threshold scores were significantly higher for the dominant ($P < 0.00$) and non-dominant ($P < 0.04$) hands among pesticide applicators when compared with scores for population based controls individually matched on age, sex, and county of residence.

Neuropsychological effects due to chronic organophosphate exposure were compared between 57 male tree fruit farmers with no history of acute poisoning, and 42 age-matched male cranberry/blueberry growers or hardware store owners (Fiedler, Kipen et al. 1997). Response rates for both tree fruit farmers and blueberry/cranberry growers were poor (39% and 14% respectively), leading to the study group being augmented with 22 hardware store owners (response rate 8%). Exposed (fruit tree growers) and control groups differed significantly in years of education and reading test scores. Exposed subjects had a significantly slower reaction time under univariate analysis. No other significant differences were noted on tests of concentration, visuomotor skills, memory, expressive language, or mood. Based on an exposure metric derived from detailed exposure histories, farmers were divided into high exposure ($n = 40$) and low exposure ($n = 59$) groups, and their neuropsychological performance was compared. Analysis of covariance with age and reading test score as covariates revealed that the high exposure group had significantly slower reaction time, dominant hand. All other (more complex) measures did not differ between groups. Since subjects underwent a large number of tests, this positive result may reflect chance. Results could also be influenced by recruitment bias arising from the poor response rate. These results may alternatively suggest that in the absence of acute poisoning, neurobehavioural effects of workers exposed to organophosphates are, at most, subtle.

A cross sectional study compared neuropsychological function in 146 sheep farmers exposed to organophosphates in the course of sheep dipping and 143 unexposed quarry workers (Stephens, Spurgeon et al. 1995). Recruitment rates were 69% for farmers (letter followed by telephone contact) and 35% for controls. Subjects completed a face-to-face series of computer assisted psychological tests and questionnaires. The farmers performed significantly worse than controls in tests to assess sustained attention and speed of information processing. These effects remained after adjustment for covariates. The farmers also showed greater vulnerability to psychiatric disorder than did the controls as measured by the General Health Questionnaire. There were no observed effects on short-term memory and learning.

The same group of subjects was also clinically examined for neurological performance. From a symptom questionnaire given immediately after dipping the 10 most symptomatic and 10 least symptomatic farmers were selected (Beach, Spurgeon et al. 1996). All agreed to participate. Several months later, each of these, along with 10 of the unexposed quarry workers from a single quarry site, underwent a standardised neurological examination similar to that which might be used in clinical practice, at a time as remote as possible from recent exposure to organophosphates so as to exclude any acute effects. Most tests showed no significant difference between the groups. Symptomatic farmers had reduced two point discrimination on the dorsum of the hand (symptomatic farmers 22 mm; asymptomatic farmers 13 mm; quarry workers 8 mm) and the dorsum of the foot (symptomatic farmers 34 mm; asymptomatic farmers 10 mm; quarry workers 11 mm) and mean calf circumference (symptomatic farmers 35.0 cm; asymptomatic farmers 36.3 cm; quarry workers 38.6 cm). However, these results may have been influenced by the selection methods and activity differences between groups. Overall, the prevalence of neurological abnormalities was low.

Other studies have suggested that subjects diagnosed with organophosphate poisoning are likely to have an increased risk of significant ongoing neuropsychological impairment (Savage, Keefe et al. 1988; Rosenstock, Keifer et al. 1991).

2.5.15 Parkinson's Disease

Studies of Parkinson's disease (PD) in the early 1980s noted that the inadvertent administration of 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) produced brain cell loss and clinical symptoms of the disease. The chemical resemblance of MPTP to some common herbicides prompted investigators to examine pesticide exposure as a possible risk factor for PD.

Many, but not all, studies since then have suggested that PD is more common among people who report exposure to pesticides in general, although no specific insecticide or herbicide has been implicated (Golbe 1998). One case study reports acute Parkinsonism after exposure to organophosphate insecticides (Senanayake and Sanmuganathan 1995). A recent study has also proposed that the risk of PD varies between different genotypes of one of the enzymes involved in pesticide metabolism, glutathione transferase (Menegon, Board et al. 1998).

A case-control study drawn from people attending a primary care centre in Detroit compared 144 subjects with Parkinson's disease with 464 controls frequency-matched for age, race, and sex (Gorell, Johnson et al. 1998). After adjusting for these variables and smoking status, there was a significant association between occupational exposure to herbicides (OR, 4.10; 95% CI, 1.37-12.24) and insecticides (OR, 3.55; 95% CI, 1.75-7.18) with PD, but no relation was found with fungicide exposure. Farming as an occupation was also significantly associated with PD (OR, 2.79; 95% CI, 1.03-7.55), but there was no increased risk of the disease with rural or farm residence or well water use. The association of occupational exposure to herbicides or insecticides with PD remained after adjustment for farming. The association of farming with PD was maintained after adjustment for occupational herbicide exposure and was of borderline significance after adjustment for occupational insecticide exposure.

In Taiwan, 120 patients with PD were compared with 240 hospital control subjects matched with patients on age (+/-2 years) and sex (Liou, Tsai et al. 1997). A structured open-ended questionnaire was used to obtain history of exposure to environmental factors, including place of residence, source of drinking water, and environmental and occupational exposures to various agricultural chemicals. After adjustment for multiple risk factors through conditional

logistic regression, there was a significant association between PD and previous uses of herbicides/pesticides and paraquat. There was no association with other variables, including source of drinking water.

A smaller case-control study examined risk factors for young-onset Parkinson's disease (YOPD) (Butterfield, Valanis et al. 1993). 63 YOPD patients were compared with 68 controls diagnosed with rheumatoid arthritis. After controlling for race, educational level, sex, age, age at diagnosis, and family history of Parkinson's disease, YOPD was positively associated with insecticide exposure (OR, 5.75, $p < 0.001$), herbicide exposure (OR, 3.22, $p = 0.033$), rural residency at time of diagnosis, past residency in a fumigated house, and nuts and seed eating 10 years before diagnosis. PD was inversely associated with cigarette smoking.

Other studies have failed to find such a clear cut association. An Italian study compared 86 patients with neurologist-confirmed PD with 86 controls similar in sex and age recruited in outpatient specialist centers of the same University Hospital (Smargiassi, Mutti et al.). Well water use and exposure to industrial chemicals were associated with PD, while cigarette smoking was “protective”. Exposure to pesticides and herbicides was similar in the two groups (OR, 1.15; 95% CI, 0.56-2-36).

130 residents of a rural Canadian city with neurologist-confirmed PD were compared with 260 randomly selected age and sex matched community controls (Semchuk, Love et al. 1992). Personal interviews were conducted to identify lifetime occupational histories. Neither interviewers, nor subjects, were blind to the subject’s status, but the underlying hypotheses were not revealed. However, since most controls were well, reporting bias cannot be excluded. Univariate analysis indicated a significant association between PD and herbicide or insecticide use, and the data suggested a dose-response relation between the PD risk and the cumulative lifetime exposure to field crop farming and to grain farming. However, when the data was analysed by multivariate analysis, previous occupational herbicide use was consistently the only significant predictor of PD risk.

2.5.16 Immunologic disturbances

A large amount of animal data suggests that pesticides may induce immunosuppression (Krzystyniak, Tryphonas et al. 1995). However, a recent review concluded that evidence that pesticides may severely impair immune functions in humans is lacking or scarce (Vial, Nicolas et al. 1996). While contact hypersensitivity is a well-identified immunotoxic effect of pesticides, it remains a rare complaint in pesticide-exposed workers. By contrast, studies of immunologically mediated systemic reactions have been generally limited to case reports.

In one small study, twelve individuals were exposed to chlorpyrifos and followed-up for 1-4.5 years to determine changes in the peripheral immune system (Thrasher, Madison et al. 1993). The subjects were found to have a high rate of atopy and antibiotic sensitivities, elevated CD26 cells ($p < .01$), and a higher rate of autoimmunity, compared with two control groups. Autoantibodies were directed toward smooth muscle, parietal cell, brush border, thyroid gland, myelin, and ANA.

The syndrome of multiple chemical sensitivity (MCS) has also been associated in some case studies with pesticide exposure. MCS appears to be poorly defined but, in essence, after acute or intermittent exposure to one or more chemicals, a person becomes sensitive to previously well tolerated, everyday, low level chemical exposures including inhalants (e.g. car exhaust, fragrances, cleaning agents) and foods (e.g. drugs, alcohol, and caffeine). Little rigorous epidemiological research has been conducted on this condition, however, MCS patients are reported to frequently have patterns of neurotoxic brain metabolism that can be confirmed on single photo emission computed tomography imaging (Ross 1997). Flinders Sensitive Line rats that have been bred to be more sensitive to organophosphates than controls, are reported to exhibit certain similarities to individuals with MCS (Overstreet, Miller et al. 1996).

2.5.17 Chromosome Aberrations

A number of small studies have suggested that pesticide exposed workers may have higher rates of chromosomal aberration than controls (Dulout, Pastori et al. 1985; Rupa, Reddy et al. 1989; Rupa, Reddy et al. 1989). Such aberrations would suggest an increased risk for cancer.

However, the relationship between chromosomal changes and the later development of cancer has not been fully determined, and other factors may have confounded the observed relationships.

2.6 SPECIFIC INSECTICIDES USED IN CATTLE DIPS

Table 3-5 shows the specific pesticides used in cattle tick dips on the North Coast of NSW since the start of the century. Essentially 4 periods of chemical usage can be identified.

- Until 1955, dips used arsenic trioxide exclusively.
- From 1955 until 1962, dips used the organochlorines DDT or, rarely, BHC.
- From 1962 until 1976, dips used a variety of organophosphates (chlorpyrifos, ethion), carbamates (carbaryl) and a formamidine (chlordimeform) as tick sensitivity varied.
- From 1976 until the present, dips have used an even broader array of insecticides: formamidines (Amitraz), carbamates (Promacyl), pyrethroids (cypermethrin, flumethrin), and organophosphates (chlorfenvinphos). The most widely used of these is Amitraz.

2.6.1 Arsenic

Arsenic is widespread in the environment and exposure from food and drinking water is unavoidable (Stohrer 1991). Arsenic has a number of acute effects, mainly thought to relate to inhibition of enzyme systems essential to cellular metabolism and resultant capillary damage, especially in the splanchnic and glomerular areas (WHO 1981). Ironically, arsenic has historically been used both as a poison and as a medication (for chronic infections such as syphilis).

Inorganic arsenic has been identified as a carcinogen in a number of population based and occupational studies (Stohrer 1991). In particular, large studies of communities drinking arsenic contaminated water have linked arsenic with skin cancer, other internal malignancies including liver, lung, bladder, and kidney cancers, and vascular disease (Wu, Kuo et al. 1989; Smith, Goycolea et al. 1998) (Tseng, Chu et al. 1968; Chen, Chuang et al. 1986). A causal relationship is supported by a recent study, which found significantly declining trends for mortality rate ratios for total malignant tumors after contamination levels were reduced (Tsai,

Wang et al. 1998). The decreases were mainly due to a fall in internal and skin cancer mortality rates. Occupational studies of workers in copper smelters exposed to airborne arsenic link the metal to lung cancer and, inconsistently, internal cancers (Lee and Fraumeni 1969; Lee-Feldstein 1983; Enterline, Henderson et al. 1987). Cancer risks identified in epidemiological studies have generally been at high exposures, and it is not yet clear whether it is appropriate to extrapolate these findings to lower levels and if so which models to use (Enterline, Day et al. 1995; Buchet and Lison 1998).

There has been limited research on the health effects of arsenic used in agriculture despite its widespread application. One study examined a cohort of 1,231 people who lived in the Washington area where lead arsenate spray was used during the first half of this century for longer periods and in larger quantities than in other areas of the United States (Tollestrup, Daling et al. 1995). This cohort had been originally defined in 1938 to determine the effects of exposure to lead arsenate spray and residue. While blood lead and urinary arsenic levels had been taken for most subjects, individual results had been lost in a warehouse flood. However, three levels of exposure (orchardist, intermediate, consumer) were defined in the original study, based upon the use of pesticide spray before and during the 1938 apple growing season. Mean arsenic and lead values were available for each exposure group. Age-adjusted hazard ratios for all causes of mortality were elevated for both male orchardists and male intermediates. The only significantly increased age-adjusted hazard ratio (1.94) was heart disease in male intermediates. No significantly elevated age-adjusted hazard ratios were observed for women in any exposure group. Two of the main weaknesses of this study are small cohort numbers and exposure classification, which is based on category from a single year's exposure history. No information on duration of employment (and exposure) was available. 8.3% of subjects were lost to follow-up and a further 30 causes of death could not be identified. Smoking history was not available.

Another study in Washington was undertaken to see if exposure to lead arsenate could explain high lung cancer rates in orchardists (Wicklund, Daling et al. 1988). All white male orchardists (n=155) who died from respiratory cancer between 1968 and 1980 were compared with 155 orchardists who died of other causes during this period. Information on occupational and

smoking data was obtained via telephone interview with next-of-kin/informants. Neither smoking habits, nor presence, intensity, or duration of lead arsenate exposure differed between case and control subjects. However, exposure history was obtained from a contact of the deceased, and 65% of controls also sprayed lead arsenate, limiting the power of the study to identify a link with this exposure.

2.6.2 DDT

Early studies of DDT were small and limited in length of follow-up and range of outcomes. In a review of animal studies in 1945 a BMJ paper concluded "there is no reason to anticipate any danger in man"(Cameron and Burgess 1945). In 1956, 51 volunteers from correctional institutions were administered large doses of DDT daily for up to 18 months (Hayes and Durham 1956). Extensive information on absorption and storage was gained and "no volunteer complained of any symptom or showed, by the tests used, any sign of illness".

Several studies in the early 1980's found associations between organochlorine levels and cancer cases at autopsy, however these were criticised on the grounds that the storage and mobilisation of DDT may be changed by the cancer process (Unger, Kiaer et al. 1982; Unger, Olsen et al. 1982).

In 1967, 59 highly exposed workers at the Montrose chemical factory in the US were examined for health status (Laws, Curley et al. 1967). Levels of DDT on fat were 39-128 times those found in the general population in another study. Status was not compared to a control group, although 8.6% of the study group had diabetes.

DDT remains so widespread in the environment that it is likely that even in the 2000's exposure to it is unavoidable. Exposure in the industrialised world has fallen dramatically since restrictions were placed on usage, however, exposure remains high in developing countries where DDT continues to be widely used in malaria control. A recent Mexican study of DDT in breast milk found mean values for the persistent DDT metabolite DDE of 0.594 ppm and estimated that 6.0% of the breast-fed babies had daily intakes of DDT above the level of 0.005 mg/kg per day recommended by the World Health Organization (Torres-Arreola,

Lopez-Carrillo et al. 1999). Samples of breast milk from 128 nursing mothers in Western Australia in 1990-91 found DDE in all samples at a median DDE level of 0.80 mg/kg, although the calculated daily intake for DDT did not exceed the acceptable daily intake of 0.02mg/kg per day for any child.(Stevens, Ebell et al. 1993) Ironically, it has also been suggested that increased levels of DDT are associated with a reduced period of lactation (Gladen and Rogan 1995).

A study of predictors of DDE in 240 US women found blood levels increased 0.17 ppb/year of age ($p = 0.0003$), presumably reflecting the importance of past exposure (Laden, Neas et al. 1999). DDE also increased 0.20 ($p = 0.02$) per 10 mg/dl serum cholesterol. Women living in the western United States had higher levels of DDE (mean = 11.0 ppb; $p = 0.003$) compared to women from other parts of the country (mean DDE = 6.3). Levels of DDE could not be predicted from consumption of meat, fish, poultry, dairy products, vegetables, fruits, and grains.

Several studies have been undertaken among DDT exposed populations. One recent study from the United States examined mortality from six different cancers by state and compared it with records of average serum DDE level adjusted for race, income and population density (Cocco, Kazerouni et al. 2000). Breast and uterine cancer mortality showed a significant inverse correlation with DDE levels in both whites and African Americans. There was an increase in mortality from liver cancer with increasing adipose DDE levels, but neither pancreatic cancer, multiple myeloma, nor Non Hodgkin's Lymphoma showed any significant correlation.

1043 deaths among men who took part in an antimalarial campaign in Italy from 1946 to 1950 were compared to mortality in the general Italian male population. DDT comprised 94% of the insecticide used during the campaign (Cocco, Blair et al. 1997). The proportional mortality ratio (PMR) for cardiovascular diseases was significantly decreased, while nonmalignant respiratory diseases showed a 22% increase in risk of borderline statistical significance. Significant increases in risk among workers exposed to DDT in application or inspection jobs were observed for liver and biliary tract cancer (PMR, 228; 95% CI, 143-345) and multiple myeloma (PMR, 341; 95% CI, 110-795). However, PMRs for liver and biliary tract cancer

were also elevated among workers who did not have direct occupational contact with DDT (liver and biliary cancer: PMR, 210; 95% CI, 117-346), suggesting this may have been related to other exposures. No trends occurred relating to length of employment in exposed jobs.

2.6.3 Other pesticides

This thesis focuses on the health impact of insecticides, however a number of studies undertaken on other pesticides are noted for completeness. In particular, a large number of studies have been undertaken on the phenoxyacid herbicides. The carcinogenic potential of these substances is thought to be linked to their contamination with dioxins and furans, and these studies have often included chlorophenols as an alternative exposure since they, too, may contain similar contaminants.

A link between phenoxy herbicide exposure and an increased risk of non-Hodgkins lymphoma has been reported with reasonable consistency by several studies (Becher, Flesch-Janys et al. 1996; Zahm 1997). Increased rates of soft-tissue sarcoma have also been reported by a number of separate studies, but not by others and evidence of an exposure-risk relationship is thought to be lacking (Lynge 1993). Studies of other cancers are limited, however, cancers of the colon, lung, nose, prostate, ovary, leukaemia and multiple myeloma as well as ischaemic heart disease have all been linked to phenoxy acid exposure (Swaen, van Vliet et al. 1992; Hooiveld, Heederik et al. 1998).

2.7 SUMMARY

Considering their common usage and the potential for widespread community exposure, the evidence available on whether or not non-acute pesticide exposure results in adverse health impacts is limited and disjointed. Even in fields where there has been extensive research, such as the possible relationship of past DDT exposure and breast cancer, the evidence is often contradictory and unclear.

A wide range of potential adverse outcomes have been linked to non-acute pesticide exposure in one or more studies. Many others have been unable to identify any significant increases in

mortality or morbidity. However, the majority of studies are seriously flawed by a range of biases, and these findings cannot individually be taken as clear evidence for or against causative relationships.

Perhaps the greatest problem confronting all pesticides research, whether it be in the form of ecological, cohort or case control studies is exposure estimation. With the exception of the organochlorines, which persist in the body and are amenable to biological monitoring, few studies exist where estimates of exposure are based on quantitative measures. In the absence of quantitative measures, studies have had to rely on surrogates for exposure such as occupation or residence. Because of the usual heterogeneity of individual behaviour and exposure in both occupational and residential settings, the ensuing misclassification bias reduces the chances of finding real associations. When this is combined with the healthy worker effect and an inability to identify all subject outcomes with certainty, there is a very strong bias in most cohort studies towards null findings. On the other hand, since many cohort studies look at a wide range of outcomes, there is also often a problem with multiple comparisons and the risk that identified associations are merely the result of chance. Cohort and ecological studies are also often influenced by the effect of unmeasured confounders such as smoking.

Case control studies have similar problems with exposure estimation and sometimes seek to overcome this using self-reported exposure measures. The potential for recall bias in such studies, particularly when subjects are not blinded to their condition, may be difficult to overcome, although many try to validate their estimates with corroborating evidence.

Because of these fundamental flaws, few conclusions can be drawn with confidence from the body of research. A number of non-fatal outcomes have been consistently reported, generally from smaller clinical studies. These include several neurological and neurobehavioural syndromes associated with organophosphates. There is also some evidence for measurable changes in immune function, but the clinical implications of these are unknown.

Of the large number of possible mortality outcomes that have been identified, those with the strongest evidence of an association with non-acute pesticide exposure are perhaps reproductive outcomes and leukaemia (although the latter may relate more to bovine mediated viruses than pesticide exposure). Less convincing associations have been suggested for breast cancer, lung cancer, Non-Hodgkin's lymphoma, multiple myeloma, pancreas cancer and prostate cancer.

The strongest research has been in the field of breast cancer, where stored blood has been used in a number of case-control studies to provide quantitative exposure estimates for organochlorines. However, even such a methodologically sound approach has failed to produce a consistent answer. After two large studies failed to demonstrate any association between organochlorines (in particular DDT) and breast cancer, a recent study developed along similar lines found a sizable and significant association.

While this style of study is likely to play an increasing role in pesticide research, such quantitative measures are generally only applicable to organochlorines. Studies into other pesticides will need to rely on surrogate exposure measures for the foreseeable future. It is difficult to imagine dramatic improvements in our understanding of this important issue without some new developments in exposure estimation, or the identification of biomarkers that can overcome some of the pervasive biases that dominate this field.

3 METHODOLOGY

3.1 OVERVIEW

This thesis describes an historical cohort study undertaken to examine the health outcomes of a group of agricultural workers with high occupational insecticide exposures. The study group comprised male staff employed by the New South Wales government between 1935 and 1995 as field workers on a program to control the spread of the introduced cattle tick. Subjects participated on a daily basis in a insecticide application program involving the running of cattle through large dip baths. Death rates in the study group were compared to those in a group of male outdoor staff from the same region who were less likely to have experienced occupational exposure to insecticides. Death rates in both groups were also compared with those of the general Australian public. Surviving cohort members were located and asked by mail to complete a questionnaire detailing both a range of non-fatal outcomes, and their exposure to possible confounding factors.

Linking health related data from different databases can potentially raise a number of ethical issues. These were considered in the design of the study and ethical clearance was gained from Institutional Ethics Committees at the University of Sydney, University of Adelaide, Northern Rivers Area Health Service, Australian Institute of Health and Welfare, and relevant state Deaths and Cancer Registries.

3.2 COHORT DEFINITION

The study population comprised a dynamic cohort divided into exposed and control subcohorts:

> *Exposed subcohort*: All male staff identified by a search of Department of Agriculture records as having worked as field officers or laboratory staff for the NSW Board of Tick Control at any time since 1935 and for whom a date of birth was recorded.
>
> *Control subcohort*: All male staff identified by a search of the records of participating local governments as having worked as outdoor field officers at any time since 1935 and for whom a date of birth was recorded; and all male office staff identified by a search of Department of Agriculture records as having worked for the Board of Tick Control since 1935, for whom a date of birth was recorded.

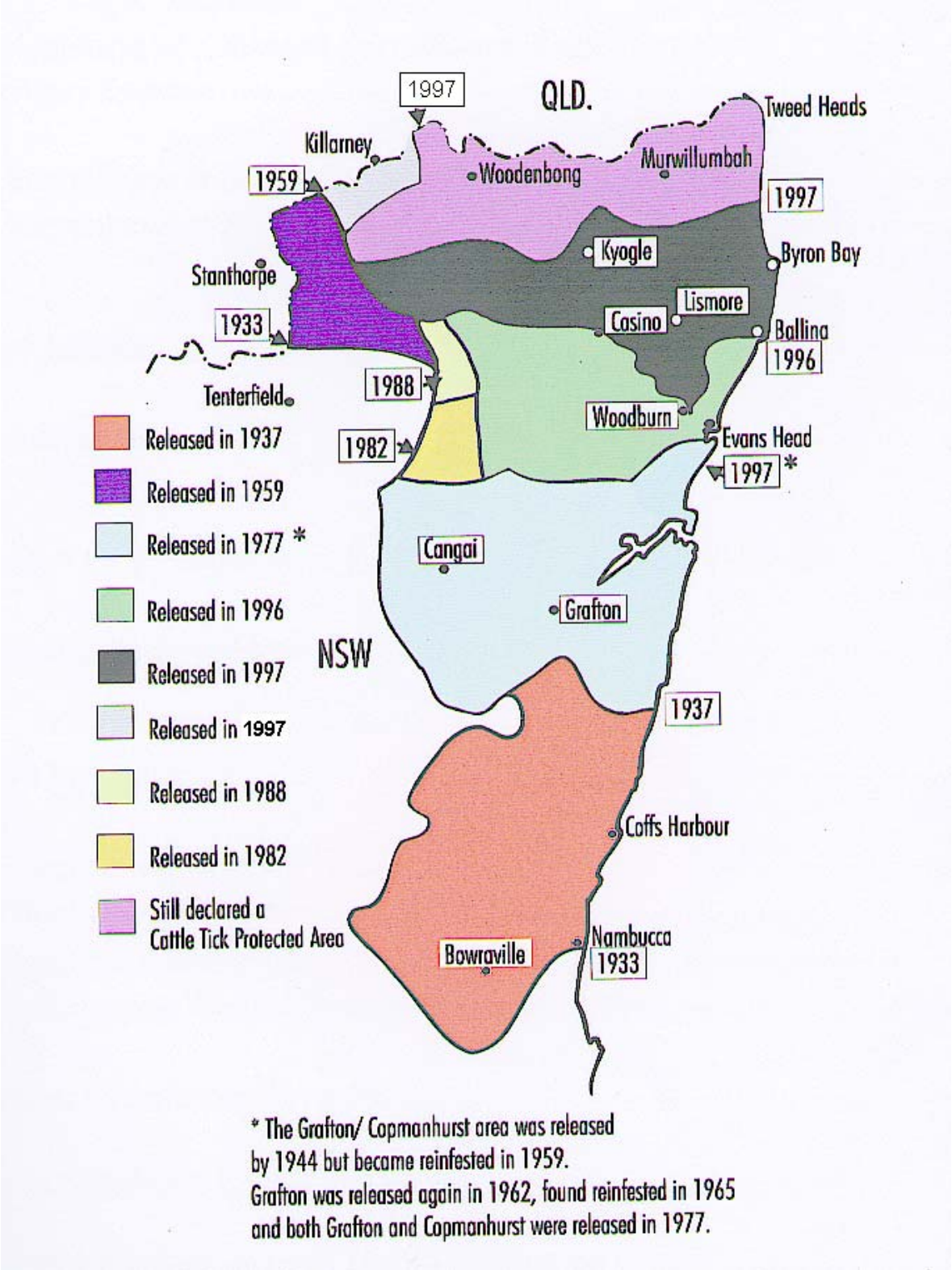
Subjects were followed from 1st January 1935 or their subsequent entry to the study until their death or 1st January 1996.

3.3 SELECTION AND ENUMERATION OF STUDY POPULATIONS

The study area was defined as any local government area on the New South Wales North Coast within which the Board of Tick Control had undertaken an organised tick control program (Figure 3-1).

Selection of the exposed subgroup involved an active search of all relevant records held by the NSW Department of Agriculture, the NSW Board of Tick Control or reported in the New South Wales Government Gazette. A number of historical records had been lost or destroyed. To avoid the possibility of selection bias, only subjects identified by record from these sources were included in the cohort. A number of other potential cohort members who had been identified by the recall of other staff or because of a noteworthy outcome but who did not meet these selection criteria were excluded. A total of 3005 subjects ("Dippers") were initially identified within the exposed subgroup. After the application of certain study criteria (see below), 2024 staff of the Board of Tick Control were included in the final analysis.

Figure 3-1 Extent of NSW Cattle Tick Program and Participating Local Government Authorities



Selection of the control subgroup was undertaken by participating local government authorities (LGAs). All 15 LGAs within the study area were invited to participate. 6 LGAs responded and provided a list of all staff on their records identified as having worked as an outdoor field officer. Several LGAs identified the specific employment categories of the staff selected. The most common categories included labourers, drivers and plant operators. A number of subjects were identified in categories that may potentially have resulted in occupational pesticided exposure such as gardeners and groundsmen. However, since the pesticide exposure of these subjects would be expected to be considerably less than that of the exposed subcohort, they were not excluded from the control category. Of the38 subjects identified as gardeners or groundsmen there were 6 identified deaths. 4 subjects died from circulatory disease, one from rectal cancer and one from an intestinal diverticulum. These deaths would not have had a significant influence on the study findings.

Table 3-1 Employment Category of Control Subjects

Category	Subjects	Category	Subjects
Assistant	3	Jackhammer man	1
Baths Manager	1	Labourer	491
Blacksmith	8	Leading Hand	8
Boilermaker	2	Lifesaver	1
Bridge Operator	4	Mechanic	35
Caretaker	21	Operator In Charge	1
Casual	19	Ordinance Officer	2
Chainman	2	Overseer	4
Crane Operator	1	Painter	12
Crusher Operator	1	Plant Operator	87
Dog Catcher	3	Plumber	10
Dragline Operator	1	Pool Attendant	7
Dredge Operator	1	Quarryman	3
Driver	65	Superintendent	1
Fire Officer	2	Saleyards	1
Fitter	1	Sign Writer	1
Foreman	3	Storekeeper	2
Ganger	51	Storeman	5
Garbage Collector	24	Street Cleaner	1
Gardener	27	Tallyman	1
Grader Driver	2	Truck Driver	16
Groundsman	11	Welder	6
Impounding Officer	2	Not Known	1002

2309 subjects were initially identified within the control subgroup. After the application of the study criteria (see below), 1959 subjects from Local Government were included in the study. The origin of all subjects included in the study is outlined in Table 3-2.

Table 3-2 Source of Subjects

LOCATION	Frequency	Percent
BOTC staff		
BANGALOW	66	1.8
BONALBO	17	0.5
CASINO	237	6.5
COPMANHURST	44	1.2
GOONDIWINDI	49	1.3
GRAFTON	175	4.8
KEMPSEY	13	0.4
KYOGLE	114	3.1
LISMORE	229	6.3
MALLANGANEE	109	3.0
MURWILLUMBAH	138	3.8
NIMBIN	8	0.2
RESEARCH STAT	64	1.8
RICHMOND	109	3.0
STANTHORPE	17	0.5
TABULUM	32	0.9
TENTERFIELD	87	2.4
TWEED	35	1.0
WALLANGARRA	10	0.3
WOLLONGBAR	31	0.9
WOODENBONG	140	3.8
OTHER	69	
Not recorded	231	
Sub-total	2024	
Council staff		
CASINO COUNCIL	77	2.1
KEMPSEY COUNCIL	230	6.3
KYOGLE COUNCIL	47	1.3
LISMORE COUNCIL	740	20.3
TWEED COUNCIL	624	17.1
ULMARRA COUNCIL	132	3.6
Not recorded	109	
Sub-total	1959	
Total	3983	

3.3.1 Selection Criteria

A total of 5314 subjects were identified in the initial cohort selection. This total was reduced after the application of a number of further selection criteria. Matching of vital status and outcome requires a known date of birth or age. 1028 subjects were therefore excluded from the study because no date of birth was noted on their employment records.

The vast majority of the initial total cohort was male. Since follow-up of women is difficult due to changing of surname with marriage, 241 female subjects and 62 subjects of unknown sex were also excluded from the study.

25 subjects identified within the exposed subgroup as office workers were reclassified to the control subgroup resulting in a final total study cohort of 3983 (1999 exposed, 1984 control).

Since a period of employment is necessary to estimate nature or duration of exposure, a further 69 subjects for whom neither the date of commencement nor termination of employment were known were also excluded in some of the analysis. As described below, where subjects had either a known commencement of employment date (n=664) or a known date of termination (n= 13), but not both, estimated durations of employment were calculated based on typical employment periods.

Table 3-3 illustrates the details of selection and culling in exposed and control groups during the cohort definition.

Table 3-3 Cohort selection

	Tick Dippers (exposed)	Local Government Staff (unexposed)	Total
Total initially identified	3005	2309	5314
Uncertain sex	46	16	62
Female	168	73	241
No date of birth	767	261	1028
Office staff reclassified as unexposed	25	(+) 25	
Final cohort	1999	1984	3983

3.4 COLLECTION OF EMPLOYMENT AND MORTALITY DATA

The study period commenced on January 1st 1935. In general, the study used subjects' employment history as a surrogate for exposure. However, the work experience of subjects who commenced employment prior to 1935 was not considered in analysis, and several staff who ceased employment before 1935 were also excluded from most of the study analysis.

When comparing mortality between groups and with the Australian population, the general analytical models used in this study allowed for a ten-year exposure "lag" period following commencement of employment, to allow for disease latency and induction (see section 3.9.4). Deaths during this period were deemed unlikely to be the result of occupational exposure. Searches of death records were therefore undertaken for the period from 1945 (ten years after the study commencement) until the study completion in January 1996.

3.5 ASSESSMENT OF VITAL STATUS

Vital status was ascertained in two ways:

The initial step involved matching the entire cohort for Medicare enrolment with the Australian Health Insurance Commission (HIC). Australian citizens are required to register with Medicare to receive a universal health care rebate. Registration ceases on the person's death (deaths notified to state death registries are forwarded to the HIC), when the person transfers to another card (for example when married), if a person changes citizenship or if they emigrate.

Medicare commenced operation on 1 Oct 1983. Cohort matching with the HIC took place in April 1995 and covered the 12 year period between these dates. For this phase of vital status assessment, subjects were deemed alive while they were enrolled with Medicare. Subjects whose enrolment ceased were deemed to have died at the end of enrolment. Subjects who were never enrolled, and for whom there was no evidence of their living after that time, were deemed to have died before October 1983.

Matching with Medicare records was undertaken by staff of the HIC based on a limited probabilistic algorithm. As explained below, this approach to matching two databases takes account of minor variations in data that may occur as details are recorded. For example, the wrong number for a day, month, or year of birth may be entered. While some discrepancies were allowed for during the HIC matching process, the algorithm used was limited compared to that used for matching against national death registries (see below), and it is likely that true matches for a number of cohort members were missed. If these subjects subsequently died, they are likely to have been identified in matching with deaths registries. However, those who remained alive at the end of the study will have been misclassified as lost to follow-up, presumed dead. As discussed below, this may have lead to an overestimation of loss to follow-up. For the purposes of analysis, such subjects were excluded on the day of their last contact with the study.

Records indicate that a number of subjects who had never enrolled with Medicare either commenced work or finished work after 1983. Many of these may represent failures to truly match cohort members with HIC records. Others may have chosen not to enroll with Medicare. For the purposes of analysis, these subjects were considered alive until their last contact with the study.

The second phase of vital status ascertainment involved matching of the cohort against the National Deaths Index (operating from 1980) and against the NSW and Queensland Deaths Registers for the period 1945-1979.

The National Death Index is a database, housed at the Australian Institute of Health and Welfare, which contains records of all deaths occurring in Australia since 1980. The data are obtained from the Registrars of Births, Deaths and Marriages in each State and Territory. The National Deaths Index (NDI) has created a matching algorithm using a probabilistic record linkage package called Automatch. Matching is undertaken using multiple passes, which group the data based on different characteristics each time (e.g. date of birth, sex, name). Two phonetic codes, NYSIIS and Soundex, are also used based on a cleaned version of each person's surname, thus allowing for variations in spellings of surnames e.g. BROWN and

BROWNE. Alternative first names e.g. Robert and Bob or Tony and Anthony, were also added to deal with variations of the same first name. Matches are then ranked according to their goodness of fit.

All possible matches were identified using this process. Since a number of the matches identified by the NDI were relatively unlikely, a further culling process was required to select those that would finally be included in the study. To ensure the final selection of matches was not biased by study subgroup, a second matching algorithm was developed locally and applied (blinded to subgroup status) to all possible matches identified by the NDI.

In some states during some periods, death notifications required a full name and age at death, rather than date of birth, as identifying information. The study algorithm therefore allowed for minor errors in names and subject ages. True matches were deemed to occur if:

1. There was no conflict of any name (although a middle name might not be recorded) and
    a. Date of birth was compatible with age at death, or
    b. Where a date of birth was recorded on the death certificate and there was one clash only of either the day, month or year of birth (maximum 1 decade error allowed)
    c. The day and month were reversed
2. There was a second name clash or minor spelling clash but the date of birth matched.

A number of possible matches falling outside this algorithm and excluded from the study may have been unrecognised true matches. Their exclusion may therefore have resulted in a possible small bias toward underestimation of mortality among both subgroups.

Matches undertaken by state deaths registries for the period 1945 to 1979 were performed by registry staff who were blinded to subgroup status. Selection required a full match of name and age, and thus may also have resulted in a bias to the null. For cost reasons, only New South Wales and Queensland registries were searched for this period. Both sub cohorts were based on the New South Wales border with Queensland, thousands of kilometres from other states. While this period of Australian history was not one of great interstate migration, a number of subjects may have moved and subsequently died interstate. In the later period of

matching covered by the National Deaths Index, 13 (1.9%) deaths occurred in states other than NSW and Queensland (Table 4-12). If this proportion was consistent for earlier years (while in fact it may well have been lower due to less interstate migration) an additional 9 deaths would have been unidentified for this period. This will have resulted in a small bias to the null.

A total of 1167 (391 control, 776 exposed) deaths were identified by this matching process.

Figure 3-2 illustrates the determination of vital status for cohort members. Of the 3983 cohort members, 2913 enrolled with Medicare. 337 of these ceased enrolment and a further 171 were matched with the National Deaths Index after October 1983, generally towards the end of the study period when HIC records would not have had the opportunity to be updated. The remaining 2405 subjects who had enrolled with Medicare were classified alive at the study endpoint 1 January 1996. Of those ceasing enrolment, death certificates were found for 328, leaving 9 lost to follow-up at their end of enrolment. These may represent people changing names, leaving the country or having died but not having been matched with death registry notifications. The high percentage of death certificates matched for those having ended Medicare enrolment (97.3%) suggests the matching process was remarkably accurate.

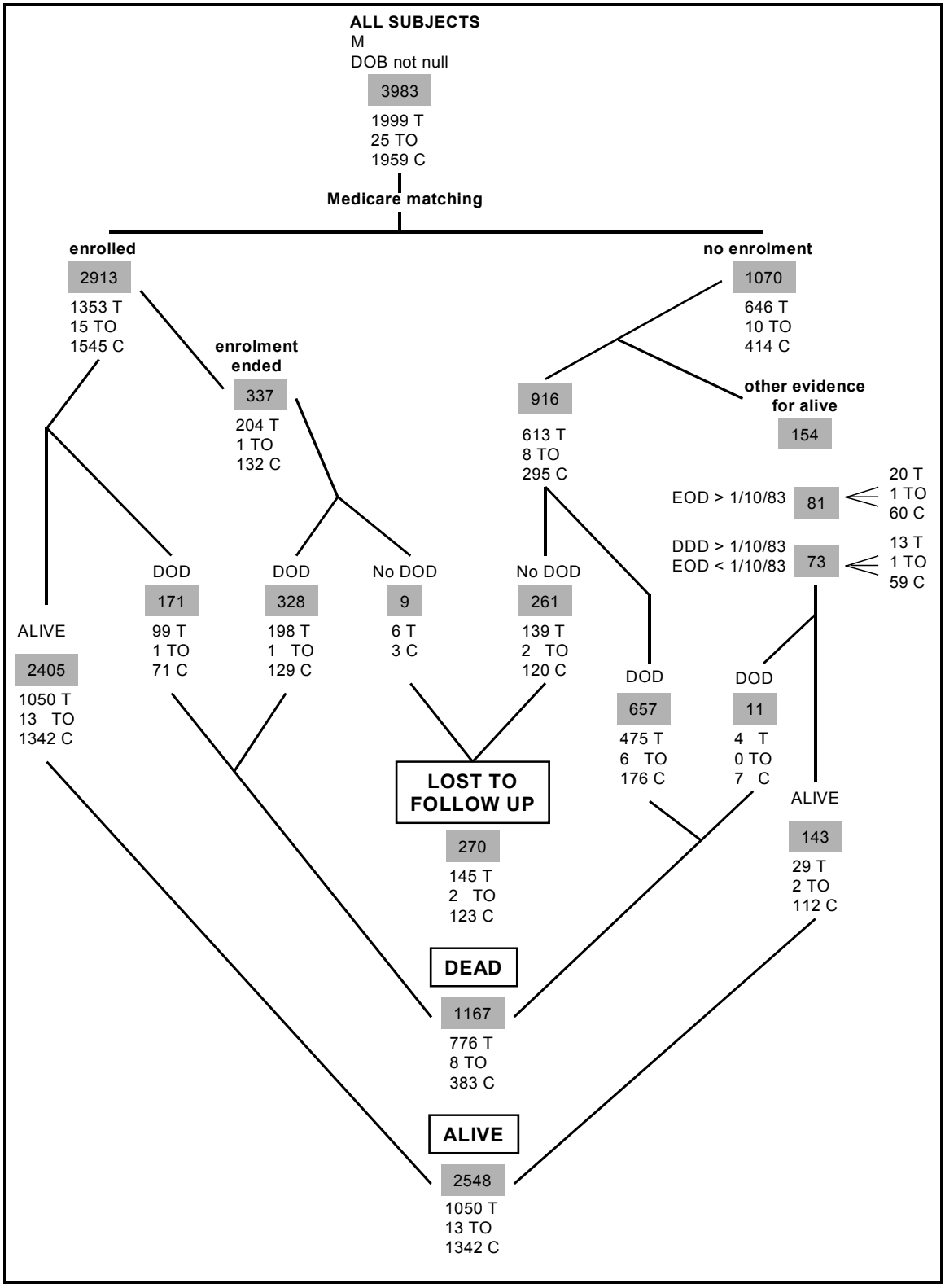
A further 1070 subjects never enrolled with Medicare. Records indicate that 154 of these subjects either commenced work or finished work after 1983. These subjects were considered to have chosen not to enroll with Medicare, or to have escaped matching, and for analysis were considered alive until their last contact with the study. Considering the accuracy of deaths matching for their contemporaries who ended Medicare enrolment, it is likely that most, if not all, deaths in this group would have been identified.

Of the 1070 subjects who never enrolled with Medicare, 666 were matched against death registers, and a further 143 were classified alive as a result of documentary evidence described above. 261 subjects remain who never enrolled with Medicare, and for whom there was neither evidence of their having been alive after 1983 nor matching with deaths registers. These remaining subjects were deemed to have been lost to follow-up. As mentioned above, an unknown number of these may simply have failed to have been matched with HIC records for clerical reasons.

A total of 261 (6.6%) cohort members who never enrolled with Medicare were therefore classified as lost to follow-up. Vital status ascertainment is therefore estimated at 93.4%, a figure considered acceptable in large cohort studies (Checkoway, Pearce et al. 1989). Of 337 subjects for whom Medicare enrolment ended and who are presumed dead, 9 (2.7%) were not matched to the National Deaths Index. Cause-of-death determination rate for the period 1983-1996 was therefore estimated at 97.3%, well above the desirable target set by the same authors of 90-95%. Since dead status prior to that time is determined by death registry notification, the determination rate for that period was 100%. In reality, some deaths were almost certainly missed and some of the subjects identified as "lost to follow-up" could be better classified as undetermined cause-of-death. This would raise the vital status ascertainment rate and drop the cause-of-death determination rate. Both would, however, remain within acceptable limits.

During analysis, subjects who were lost to follow-up were included in the study until the last date their vital status was known, for example when they left employment or ceased enrolment with Medicare. These subjects were excluded from the study after that date.

Figure 3-2 Ascertainment of Vital Status



Note: T denotes Tick Dipping Staff; TO denotes Tick Office Staff, C denotes Controls

3.6 CAUSE OF DEATH

Coding the causes of death identified on death certificates was undertaken by nosologists trained in the rules specified by the International Classification of Diseases (ICD) 4-9th revisions compiled by the World Health Organisation (Organisation 1991). For the period 1980- 1996, when the cohort was matched against the National Deaths Index, a single underlying cause of death was identified for each subject by the Australian Bureau of Statistics (ABS) prior to matching.

Matching with state deaths registries for the period prior to 1980 provided death certificates with up to 4 possible causes of death. To avoid bias, these certificates were referred to the ABS, and an underlying cause of death identified in the ICD code in use at the time of death. These were then converted to the relevant ICD9 code. This allowed a valid comparison of the cohort with national benchmark death rates adjusted for year of death within the person-years analysis. For this period also, appropriately trained research staff associated with the study but blinded to study subgroup, identified ICD9 codes for all 4 causes identified on the certificate. This enabled all 4 causes of death to be searched when making internal comparisons of mortality outcomes between subgroups.

3.7 MORBIDITY DATA

An attempt was made to locate the 2548 cohort members who were thought to be still alive in 1996. These subjects were either enrolled with Medicare at the completion of the study, or alternative evidence existed suggesting that they were alive despite never having enrolled with Medicare (see above). The names of these subjects were matched against the electoral roll for districts covering the tick quarantine area, and against relevant telephone directories. Dates of birth were not available from the electoral roll to reinforce this matching. Possible contact addresses were found for a total of 1533 subjects using this process.

All 1533 subjects were mailed a comprehensive questionnaire and information sheet (Appendix 1) and asked to complete and return it by mail. Subjects who did not wish to participate in this part of the study were given the option of returning a blank questionnaire.

To minimise potential recall bias, subjects were advised the study, titled "The North Coast Outdoor Workers Study", was exploring the impact on subjects' health of a range of factors relating to outdoor work.

Questions focused on factors that might potentially confound the broader study, such as smoking or alcohol consumption, a work and pesticide exposure history, and a range of non fatal outcomes that may be related to pesticide exposure. Key components of the questionnaire are shown in Table 3-4.

Table 3-4 Topics covered by survey of surviving cohort members

Work history
Pesticide exposure history
Educational history
Smoking history
Alcohol history
Neuropsychological state (Hogstedt 16)
Reproductive history
Specific outcomes including:
Asthma
Diabetes
Circulatory disease
History of amputation
Skin cancer
Chronic fatigue syndrome
Parkinson's disease
Birth defects in offspring

The initial response to the mail-out was poor. Non-responding subjects were then followed up by telephone and reminded about the project. The response to the questionnaire mail-out and follow-up is outlined in the results section. The total response rate for the questionnaire was 54.9%, with a further 17% choosing to return a blank questionnaire. Dippers (60.9%) were more likely to respond than controls (51.6%), although the percentage of dippers and controls choosing to return a blank questionnaire was almost identical. Since a large proportion of the

subjects failing to return a questionnaire could also not be contacted by phone, this low response rate may largely reflect incorrect mailing addresses due to subjects changing address after the creation of the electoral roll or telephone directory.

3.8 EXPOSURE DATA

The Board of Tick Control maintained accurate records describing the chemicals used in dips during the study period. While these records identify the precise chemicals in use at each specific dip at any point in time, the records do not identify which staff were working at which dip on specific days. Chemical usage did, however, follow defined patterns (Table 3-5). Until 1955, only arsenic trioxide was used in dips. After 1955, a program commenced replacing arsenic with DDT. Dips were drained by hand, and arsenic was replaced by DDT or sometimes the related organochlorine, BHC. By 1961 most dips contained DDT. In 1962, DDT was drained from all dips and since that time a range of different insecticides have been used including organophosphates, carbamates and pyrethroids. Many of these are still widely available. For the purposes of analysis, these periods have been categorized into the period of arsenic use (1935-1955), the period of DDT use (1955-1962), and the period of modern chemical use (1963-96).

The modern chemical period itself can also be broken down into two distinct eras: pre and post 1976. Before 1976, the main chemicals used were carbaryl, coumaphos, chlorpyrifos, dioxothion, ethion and chlordimeform. After 1976 these were replaced by cymyazole, amitraz, promacyl, cypermethrin, chlorfenvinphos and flumethrin. To ensure adequate numbers for statistical analysis, both these sub-periods have generally been collapsed into one exposure period for comparisons of cohort mortality. However, where possible associations have been identified, the two sub periods have been distinguished in an effort to identify specific chemicals that may be responsible.

Table 3-5 Chemicals used in cattle dips during different periods and the classification used in this study (after Beard et al)

Tickicide	Period of Use	Classification
Arsenic (Trioxide)	-1955	*Period of Arsenic Use*
DDT	1955-1962	*Period of DDT Use*
BHC	1955-1962	
Carbaryl	1963-1970	
Coumaphos	1962-1965	
Carbophenothion	1962	*Early Period of*
Chlorpyrifos	1969-1974	*Modern Chemical Use*
Bromophos ethyl	1969?	
Dioxothion	1962-1976	
Ethion	1962-1976	
Chlordimeform	1973-1976	
Cymyazole	1977-1986	
Chlormethiuron	1977	
Amitraz	1976-present	*Late Period of Modern*
Promacyl	1977-present	*Chemical Use*
Cypermethrin	1979-present	
Chlorfenvinphos	1979-present	
Flumethrin	1986-present	

The Board of Tick Control (BOTC) did not maintain a formal occupational hygiene program during much of the study period, and maintains no records of any biological or environmental assessments of staff exposures. Anecdotal reports, however, suggest exposure of staff to these insecticides was extremely high and regular.

BOTC staff were allocated a number of dips to work on. Many dips were in remote areas most easily accessible by horse, and field staff were often required to camp at the site during the working periods. During such periods access to washing facilities was limited. Staff were required to maintain the concentration of baths at specific levels and took regular samples, preparing and adding further concentrated insecticide as required. For DDT this required the melting of solid DDT in a campfire "billy" prior to its addition to the dip. The dipping process itself was a period of high exposure as staff wore little protective clothing, were repeatedly splashed by treated cattle and report periodically jumping in the bath themselves to extricate recalcitrant or juvenile animals. Treated cattle also soiled dips with dung and hair, which was required to be regularly scooped from the bath. Interviews with ex-staff suggest that when

returning home their wives would often complain that they "stunk of chemicals" for some time afterwards.

In general, control staff were not exposed to pesticides at work, having roles at sewerage treatment works, bridge maintenance, and road works. During later years of the study, some control subjects may have used herbicides for the control of roadside weeds. Since all subjects lived in a rural area, it is likely some Dippers and controls also faced pesticide exposure at home.

During the early 1980's the NSW Department of Health, through its occupational work program, traveled rural areas offering free biological monitoring for insecticide exposure to interested community members. Original records of this program have been destroyed, however one Departmental staff member maintained an independent computer database of results of this program. The cohort was matched against these records, and a number of cohort members appear to have taken up this offer. Sampling was limited, but included total serum DDT levels. While DDT use had stopped at least 18 years prior to this sampling period, DDT metabolites have a long half-life in humans, and the DDT metabolite DDE (included in total DDT results) is a good indicator of past exposure (Beard, Marshall et al. 2000).

1220 subjects were tested during the program with a median serum total DDT and metabolites of less than 5μg/L (ppb). Participants in this testing program would generally have a history of some pesticide usage either at home or at work, and the overall results would be expected to be higher than for the broader community. However, the median DDT level of participants is comparable with a mean serum DDE level reported in a sample of 85 White persons from rural parts of the United States of 5.03ppb (Stehr-Green, Farrar et al. 1988).

Verbal reports suggest that control subjects would have been unlikely to be exposed to DDT at work and their total serum DDT at the time of the testing program would have been expected to reflect typical exposures within the broader population. Similarly, members of the exposed cohort who did not work between 1955 and 1962 would be expected to have DDT exposures

similar to the rest of the population. Dippers working during this period of DDT usage would, however, be expected to have higher than average exposures.

A total of 25 cohort members were matched to the monitoring program. The serum DDT levels of cohort members are shown in Table 3-6. Unfortunately, only three dippers who had worked during the DDT era could be matched. In relation to the results from all subjects in the testing program, the DDT levels of these subjects were high, very high and exceptionally high. Two dippers worked for the whole of the DDT period. One was tested in 1981 at the age of 64 and had a serum DDT of 80 ppb, one of the highest results in the whole sampling program. The other was tested in 1980 at the age of 64 and had a serum DDT of 10 ppb. The other Dipper, tested in 1981 when he was 53, had worked for only one year and showed a serum DDT of 28 ppb. DDT exposed Dippers therefore had a mean total serum DDT of 39.3 ppb. These samples were taken a minimum of 18 years since last exposure and can be expected to have fallen considerably due to metabolism and excretion over that period. Mean DDT levels in exposed Dippers were over five times that of members of the control subcohort (6.7 ppb) and eight times that of Dippers who did not work during the DDT era.

Table 3-6 Results of biological monitoring 1980-87

	Number	Mean total serum DDT (ppb)	Range
All sampling program subjects		95% CI	
Controls	14	6.7	0-14
DDT exposed Dippers	3	39.3	10, 28, 80
Other Dippers	8	4.25	0-11

3.9 ANALYSIS

3.9.1 Reference populations

As discussed in the literature review, the Healthy Worker Effect poses a major problem when comparing an occupational cohort with external reference populations. This effect tends to wane with duration of follow-up (Breslow and Day 1987). This study was designed to allow comparison of the exposed cohort with two reference populations: the Australian population as a whole, and a control subcohort selected from outdoor staff from a similar region and socio-

economic background, but generally not occupationally exposed to insecticides. For studies where subcohorts can be distinguished in terms of their exposure, most weight in the interpretation is often given to comparisons between subgroups within the cohort (Breslow and Day 1987).

3.9.2 Duration of employment

In this study, a subject's period of employment has been used to estimate both the type of chemical he was likely to have been exposed to, and the length of time over which that exposure took place. Since there is no biological or environmental data to allow determination of the actual exposures faced by individuals, the duration of exposure to a chemical, or range of chemicals, has been used as a surrogate for exposure dose.

Most subjects (n=3237) had recorded dates for commencement and termination of employment. A small proportion (n=69) had neither date reported on their records and these subjects were excluded from all analysis requiring an estimate of exposure duration. 664 subjects had a known commencement of employment date but no known date of termination, and a further 13 had a known termination date but no known date of commencement.

In general, analysis was limited to subjects with known dates for both commencement and termination of employment. However, so as not to lose the information available on other subjects, in some identified parts of the analysis, estimated durations of employment were calculated based on typical employment periods. The average durations of employment (days) were calculated for both exposed and control subjects and the missing employment dates were estimated by counting forward or back from the known employment date. Thus, for those for whom only a commencement date was known, a termination date was estimated by adding the mean duration of employment of their subcohort. For those where only a date of termination was known, an estimated commencement date was calculated by subtracting the mean duration of employment of their sub cohort.

Using estimated dates of employment has the potential to influence the study findings in both positive and negative ways. By retaining as much data as possible within the analysis, study

power is increased. However, since most of the subjects will have had shorter or longer periods of employment than those estimated, precision is reduced. The impact of these estimations on SMR's was examined during analysis. The results suggest the influence of including estimated duration of employment was minor (see Results), and the bulk of the analysis was therefore limited to subjects on whom all data was available.

3.9.3 Data Entry

All data collected during the study was entered into a Microsoft Access database before importing into SAS for analysis (SAS/STAT version 6.1. SAS Institute Inc.). Data entry on key variables such as underlying cause of death was cross-checked and found to be accurate for all but a few minor errors.

Data on Australian deaths was obtained from the Australian Institute of Health and Welfare. This data was stratified by sex, 5 year age group and calendar year and was linked to similarly grouped data on the Australian population.

3.9.4 Latency

Latency has been defined as the period from disease initiation to manifestation, while the period between first exposure to an agent and disease initiation has been termed the induction time (Rothman and Greenland 1998). The implication of these two related concepts is that there is a lag period between when a subject is exposed and when this exposure may cause a death or cancer. Any death or cancer identified in the intervening period could not be due to the exposure and should be excluded from analysis.

To account for this, an exposure lag period has been factored into the analysis. There is no standard lag used for analyses such as this, although round figures are commonly used (B. Armstrong, personal communication). As the follow-up period for this study is relatively long, a default exposure lag of 10 years was chosen in advance of analysis and has been used throughout the study. This lag period results in a subject's current year at risk being assigned

their cumulative exposure of 10 years earlier. For example, an exposed subject commencing work in 1955 will not be considered to have any cumulative exposure until 1965 when their cumulative exposure will be calculated at 1year.

Thus an exposed subject did not start to contribute person years to the follow-up until the 10 year exposure lag was passed, and deaths occurring in exposed subjects within 10 years of commencing work (or exposure to a specific chemical under study such as DDT) were not counted as observed deaths in analyses of mortality in the exposed groups. However, mortality of these subjects was analysed and reported in a separate "control Dipper" exposure subgroup. To ensure validity in comparisons between Dippers and the external, council derived, control group, this same approach was also used in analyzing their mortality.

The impact of using different lag periods in the analysis was also examined for key outcomes and is included in the results section.

3.9.5 Data Analysis

A program incorporating person-years analysis was developed in SAS, based on a published model by Pearce and Checkoway (Pearce and Checkoway 1987). Data generated by the program was checked against the original database to ensure its consistency.

This program created a record for each person-year of follow-up. Key temporal variables in the program included date of birth, dates of commencement and termination of employment, and dates of commencement and termination of follow-up (whether that be study endpoint, death or last known contact date).

Follow-up was defined as starting either at the date of study commencement (for most analyses 1935) for subjects starting work prior to that date, or at the subject's commencement of employment. For subjects not lost to follow-up, termination of follow-up was defined as being either their date of death or the study endpoint (December 1995). If a subject was lost to follow-up they were deemed to be alive until their last recorded contact with the study. Such

contact included termination of employment, registration or termination of enrolment with Medicare, and diagnosis of cancer notified to the National Cancer Statistics Clearing House.

Cumulative duration of employment was calculated for each subject and this information was used to categorise subjects into exposure groups (usually less than 5 years, 5-15 years, and greater than or equal to 15 years of exposure).

Person-years data were generated for each subject by considering each year of follow-up in turn and creating a separate record with appropriate values for covariates including year at risk (in 10-year groupings), length of follow-up, age at risk (in 10-year groupings) and cumulative duration of employment (generally in 3 categories). Deaths and person years counts were then aggregated by covariate categories and this data used as the basis for Poisson regression and calculation of Standardised Mortality Ratios.

3.9.6 **Calculation of Standardised Mortality Ratios**

Standardised Mortality Ratios (SMRs) were calculated by firstly summing the number of observed deaths for each subcohort across calendar year and 10yr age group strata. The SMR denominator was obtained by multiplying the specific rates for the same strata in the reference Australian population by the corresponding number of person-years in the exposed subcohort and then summing across all strata. Exact Poisson confidence intervals were set around these SMRs using a published method developed by Daly (Daly 1992).

A range of models were used for external analysis. The default model followed all subjects from 1935 to 1995 inclusive, incorporating a lag period of 10 years and excluding all subjects for whom complete information was not available. However, the influence of different lag periods on SMR was also modelled for some outcomes.

As described previously, a large number of the cohort had all details bar the date of leaving employment. The default analysis excluded these subjects. However, to ensure the information available on these subjects was not wasted, durations of employment were

estimated for them based on their commencement date and the mean duration of employment for tick staff or controls. The results of analysis using these estimated durations of employment were compared with other results.

3.9.7 Internal comparisons

A person-years method was also used to calculate Standardised Incidence Ratios using Poisson regression to compare deaths in the exposed subcohort or different exposure subgroups with deaths in the control subcohort. For rare outcomes, the numbers used to determine the denominator in these calculations (i.e. the direct rate in council workers) may be quite small. In these cases, the estimate does not necessarily have a low error variance. To allow for this sampling variability in calculating Standardised Incidence Ratios, confidence intervals were calculated using likelihood ratio based methods.

The construction of likelihood ratio-based confidence intervals is derived from the asymptotic χ^2 distribution of the generalized likelihood ratio test and is thought to be more robust than classical approaches when the sample size is small (Venzon and Moogavcar 1988). The program starts at the maximum likelihood estimate. The log likelihood function is approximated with a quadratic surface, for which an exact solution is possible. The process is iterated until convergence to an endpoint is attained. The process is repeated for the other endpoint.

Common outcomes with large numbers of deaths allowed both age at death (specifically the log of the midpoint of 10 year age groups) and the influence of changing death rates at different times during the follow up period (whether subjects worked before or after 1960) to be included in a multivariate analysis adjusted for the log of person years of follow-up. This approach was used for total deaths, and for deaths from circulatory disease, cardiovascular disease and total cancers.

Because of limitations resulting from small numbers of events, for the internal comparison of less common outcomes, the multivariate Poisson regression was limited to exposure subgroup and age.

Despite the analytical strategies used to account for small numbers in the mortality estimates in the control population, SIRs for uncommon conditions are susceptible to the influence of sampling variability in this group. In general, the approach taken throughout this study is to assess possible associations from the weight of evidence generated from all available sources of information. SIR estimates need to be viewed in light of the evidence on mortality generated by comparison to the Australian population. Where significantly elevated SIRs are not supported by evidence from SMR analysis, they need to be viewed with some scepticism, particularly for rarer outcomes.

3.9.8 Analysis of survey of surviving cohort members

Questions in the survey distributed to surviving cohort members generally required binary responses. Analysis of the questionnaire was therefore undertaken using logistic regression comparing the odds of a particular outcome in the exposed and control subgroups. The multivariate regression model also included log of subject age, and adjusted for possible confounding from smoking by including a categorical predictor variable based on whether subjects reported ever having smoked.

For analysis involving continuous outcome variables (number of years at school and score on a neuropsychological screening questionnaire), analysis was undertaken using Analysis of Variance, adjusting for age.

4 RESULTS

4.1 DESCRIPTIVE INFORMATION

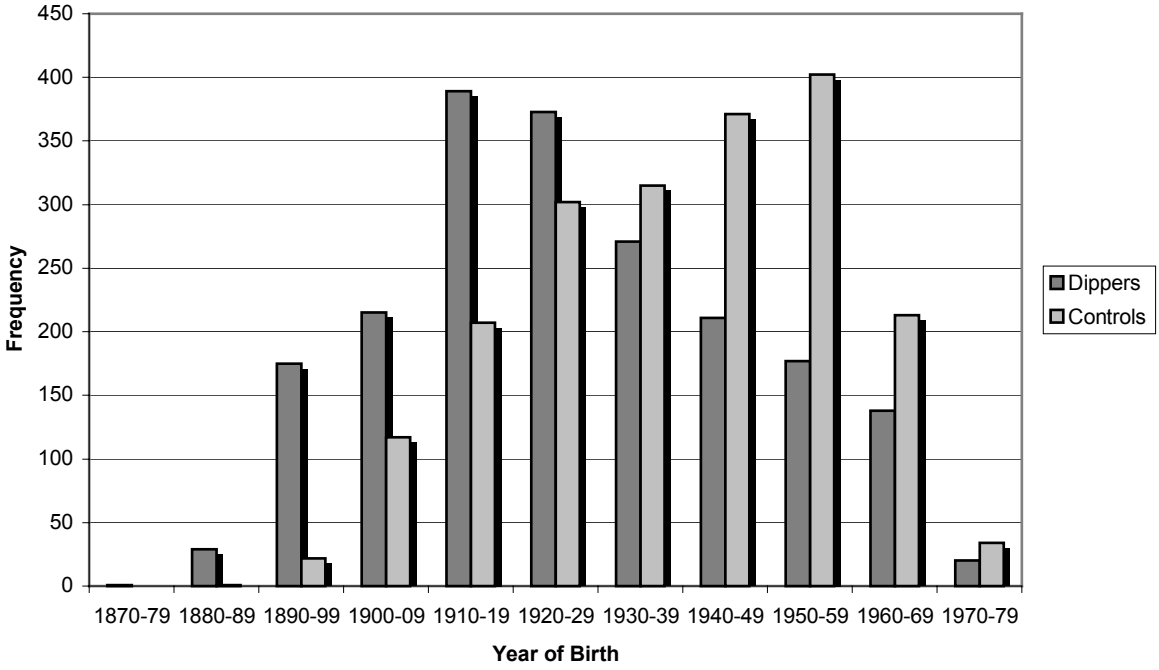
4.1.1 Subject dates of birth

After defining the cohort using the criteria outlined in the Methods section, a total of 3983 subjects were included in the study. Dates of birth ranged from 20 September 1874 to12 July 1975. The age distribution of the two study groups is displayed in Table 4-1and Figure 4-1.

Table 4-1. Year of birth of study subjects

	All subjects		**Dippers**		**Controls**	
Year of Birth	Frequency	Percent	Frequency	Percent	Frequency	Percent
1870-79	1	0.0	1	0.1		
1880-89	30	0.8	29	1.5	1	0.1
1890-99	197	4.9	175	8.8	22	1.1
1900-09	332	8.3	215	10.8	117	5.9
1910-19	596	15.0	389	19.5	207	10.4
1920-29	675	16.9	373	18.7	302	15.2
1930-39	586	14.7	271	13.6	315	15.9
1940-49	582	14.6	211	10.6	371	18.7
1950-59	579	14.5	177	8.9	402	20.3
1960-69	351	8.8	138	6.9	213	10.7
1970-79	54	1.4	20	1.0	34	1.7
Total	3983	100	1999	100	1984	100

Figure 4-1 Frequency Distribution of Subject Dates of Birth by Sub-cohort



While the range of dates of birth for each group was similar, the peak for dippers was around 1910-1930, while for controls the peak was 1940-1960. When ages at study completion (31 December 1995) were calculated for subjects from their date of birth regardless of their real vital status, there was a significant difference ($P < 0.001$) between the mean age of Dippers (68.9 yrs) and the mean age of Controls (56.9yrs).

4.1.2 Employment History

Dates of commencement of employment ranged from 15 Jan 1908 to 31 Oct 1994. 175 subjects finished employment before the study period. There was no significant difference (P= O.48) between the mean duration of employment for Controls (4616 days) and the mean duration of employment for Dippers (4453 days) (Table 4-2). The distribution of duration of employment was also very similar for the two groups (Table 4-3). More than 25% of both dippers and controls worked for over 20 years. More than 25% also worked for less than 3 years. However, just as Dippers tended to have an earlier date of birth, so Dippers in the study tended to commence employment earlier than controls.

Table 4-2 Mean Duration Of Employment (Days) For Dippers & Controls Subjects

GROUP	Obs	Min	Max	Mean	Std Error
Controls	1703	1.0	19415	4617	95.3
Dippers	1654	2.0	16886	4454	103.1

Table 4-3 Duration of employment (quartiles) for controls and dippers

	Controls years (days)	Dippers
100% (Maximum)	53.2 (19415)	46.3 (6886)
75%	20.1 (7366)	20.2 (7392)
50% Median	10.4 (3824)	8.4 (3078.5)
25%	2.7 (969)	1.7 (618)
0% Minimum	1	2

As described in the Methods section, a range of different chemicals were used during the study period. While there was usually a transition period between tickicides, 3 different chemical periods could be identified: the period of arsenic use (<1955), the period of DDT use (1955-1962) and the period of modern chemicals use (>1962). These distinct periods provided the opportunity to examine the influence of different phases of chemical usage on mortality. The period of modern chemical use, itself, can be further subdivided into different periods: before and after 1976. To ensure adequate numbers for statistical analysis, both these sub-periods have generally been collapsed into one exposure period for comparisons of cohort mortality. However, where possible associations have been identified, the two sub periods have also been analysed separately in an effort to narrow down the range of chemicals that might be responsible.

Exposed subjects were categorised by their period of employment as a surrogate measure for their insecticide exposure. Subjects were only allocated to one of these specific chemical categories if they had full documentation on commencement and termination of employment (see below). Because many subjects retained their employment for long periods, the majority tended to work during more than one era of chemical use. Table 4-4 shows the number of subjects in both subcohorts working during different chemical periods. Only a small number of Dippers or controls worked exclusively during the arsenic or DDT periods. However, a large number worked only during the era of modern chemicals.

Table 4-4 Number of subjects working during different chemical periods

Period	Number of subjects working exclusively during this period	Number of subjects working at all during this period
Arsenic use	5 (1 Controls, 4 Dippers)	528 (199 Controls, 329 Dippers)
DDT use	144 (24 Controls, 120 Dippers)	579 (185 Controls, 394 Dippers)
Modern Chemical use	2100 (1257 Controls, 843 Dippers)	2949 (1586 Controls, 1363 Dippers)

For the purposes of this analysis, Dippers working before 1955 were assumed to have faced occupational exposure to arsenic, and dippers working between 1955 and 1962 were assumed to have faced occupational exposure to DDT. Since the numbers of subjects working exclusively within these periods were small, subjects were included in these two categories regardless of whether they may have worked in other periods or not.

Since the number of subjects who commenced employment after 1962 was relatively large, the third category of exposure to modern chemicals was restricted to Dippers who only worked during the period of modern chemical use. For some analyses this was further divided into subjects working before or after 1976. These subjects may also have worked during the other modern chemical period.

Controls comprised council or administrative staff working during the same period. A separate, "control Dippers", subgroup comprised Dippers who had not overcome the 10 year exposure lag restriction (i.e. who had died less than 10 years after their commencement of employment). This group of subjects cannot be considered as true controls since they faced occupational exposure and it is unlikely the 10 year lag has a dichotomous influence. Nevertheless, they provide a second useful comparison group when interpreting the study findings. When mortality was being analysed for specific chemical periods, this "control Dippers" subgroup also included mortality among Dippers who may have worked in earlier or later chemical periods. For some rarer outcomes, including the "control Dippers" group

sometimes prevented convergence of the statistical model used to compare mortality among Dippers and controls. On these occasions this group was excluded from the analysis.

4.2 MORBIDITY

As described in the Methods section, surviving cohort members were invited to participate in a questionnaire survey of different outcomes and behaviours.

4.2.1 Survey Response Rates

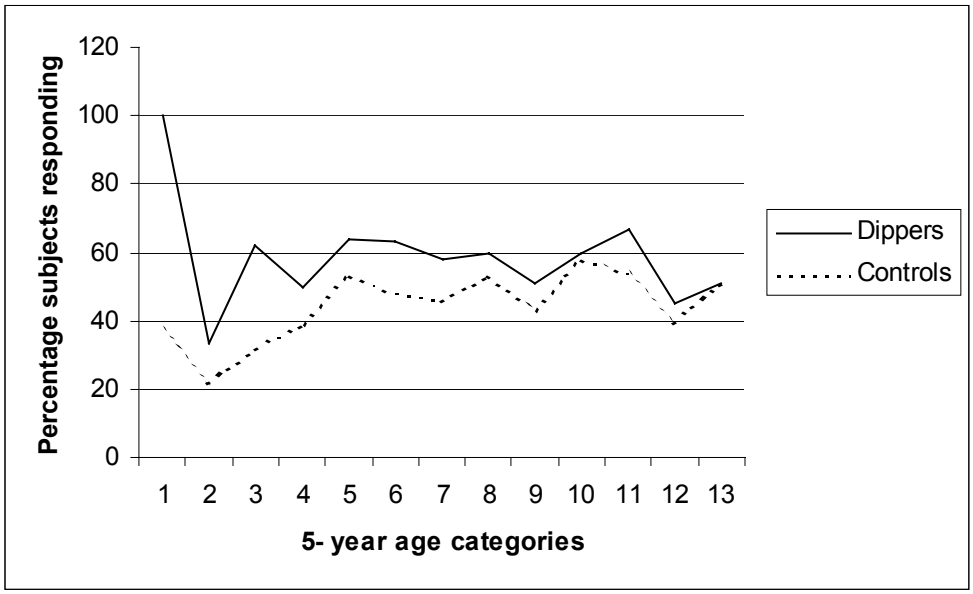
Possible contact addresses were identified for a total of 1533 surviving subjects (540 Dippers and 993 controls) by searches of local electoral rolls. All subjects with addresses identified in this way were mailed the survey questionnaire and an information sheet. Non-responding subjects were matched against local telephone directories and repeated efforts were made to contact them by phone and encourage them to participate in the study. A total of 841 subjects (329 Dippers and 512 controls) completed and returned the questionnaire (Table 4-5). A further 260 subjects (91 Dippers and 169 controls) chose to return the questionnaire blank, indicating they did not wish to participate in the survey. The percentage of Dippers (16.9%) and controls (17.0%) choosing to return a blank questionnaire was almost identical. 432 subjects did not respond to the questionnaire (120 Dippers and 312 controls).

Table 4-5 Response rate for morbidity survey

	Dippers (% dippers matched)	Controls (% controls matched)	Total (% total matched)
Subjects matched with Electoral Roll and telephone directory	540	993	1533
Subjects completing questionnaire	329 (60.9%)	512 (51.6%)	841 (54.9%)
Subjects returning questionnaire blank	91 (16.9%)	169 (17.0%)	260 (17.0%)
Subjects failing to return questionnaire	120 (22.2%)	312 (31.4%)	432 (28.2%)

Response rates varied with age, and Dippers had a higher response rate than controls across all 5-year age categories (Figure 4-2). When the response rate of Dippers and controls was compared across 5-year age categories using Mantel-Haenszel analysis, this difference was significant (p= 0.001).

Figure 4-2 Response rates for Dippers and Controls across 5-year age categories



4.2.2 Characteristics of Exposed and Control Groups

When reported time at school of Dippers and controls was compared, most subjects spent 10 years at school (Figure 4-3), with responding Dippers having, on average, spent 8.7 years at school and controls spending a mean of 9.1 years. When examined using Analysis of Variance and adjusting for age, this difference was significant (Table 3-2).

Figure 4-3 Reported years of schooling in responding subjects

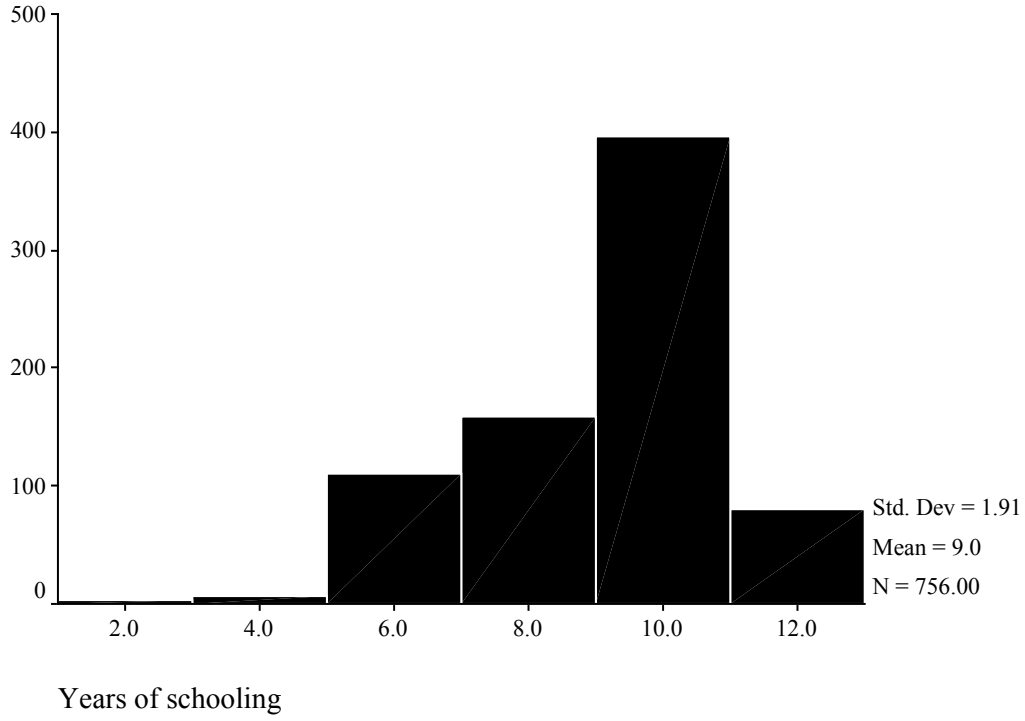


Table 4-6 Analysis of Variance between subject group and years of schooling adjusted for age

Tests of Between-Subjects Effects

Dependent Variable: Years of schooling

Source	Type I Sum of Squares	df	Mean Square	F	Sig.
Corrected Model	671.042[a]	2	335.521	121.897	.000
Intercept	57361.666	1	57361.666	20839.873	.000
AGE	642.777	1	642.777	233.525	.000
GRP	28.265	1	28.265	10.269	.001
Error	1976.292	718	2.752		
Total	60009.000	721			
Corrected Total	2647.334	720			

a. R Squared = .253 (Adjusted R Squared = .251)

When age adjusted responses were compared using logistic regression, there was no significant difference between current smoking in either group (OR 1.20; 95% CI 0.83-1.73).

Respondents from the Dipper subcohort were, however, significantly more likely to report ever having smoked (OR 1.66; 95% CI 1.21-2.28). There was no statistically significant difference in alcohol drinking patterns between the two groups.

Table 4-7 Relationship between subject group and self reported behaviours.

	Odds Ratio	Lower Confidence Limit	Upper Confidence Limit	PVAL
EVER DRINKER	1.47	0.85	2.54	0.16
CURRENT SMOKER	1.16	0.80	1.68	0.43
EVER SMOKER	1.66	1.21	2.28	<0.01

Note: Logistic regression by group (Dipper or control) adjusted for log age, ever smoked

4.2.3 Self Reported Occupational Pesticide Exposures

Subjects were asked to indicate whether they had ever used pesticides as part of their work and, if so, which ones. Table 4-8 shows positive responses by subcohort and the odds ratios for occupational pesticide use by Dippers compared to controls. Surviving Dippers were significantly more likely to report using pesticides occupationally (OR 10.39; 95% CI 6.15-17.54). The odds were greatest for carbamates and pyrethrins, which are the main insecticides currently used in cattle dipping. The odds were lowest for fungicides and herbicides.

Table 4-8 Odds ratios for occupational use of different pesticides.

	Controls reporting use	Dippers reporting use	ODDS RATIO	Lower Confidence Limit	Upper Confidence Limit	P VALUE
Any Pesticide	323	326	**10.39**	**6.15**	**17.54**	<0.01
Arsenic	62	110	**3.44**	**2.37**	**5.01**	<0.01
Organochlorines	115	155	**2.96**	**2.15**	**4.07**	<0.01
Organophosphates	106	180	**4.62**	**3.37**	**6.33**	<0.01
Carbamates	77	195	**9.08**	**6.44**	**12.80**	<0.01
Pyrethrins	69	188	**10.77**	**7.46**	**15.54**	<0.01
Herbicides	265	180	**1.36**	**1.01**	**1.83**	0.04
Fungicides	59	29	0.77	0.48	1.25	0.29

Note: Logistic regression by group (Dipper or control) adjusted for log age, ever smoked

4.2.4 Self Reported Morbidity

The responses of Dippers and controls to a range of questions on possible adverse health outcomes were compared using logistic regression adjusted by age and smoking behaviour (Table 4-9). A number of significant associations between reported outcomes and cohort group were identified. These included suffering from asthma (OR 1.61; 95% CI 1.06-2.46) or eczema (OR 1.61; 95% CI 1.02-2.55) or having a child with asthma (OR 1.47; 95% CI 1.02-2.12).

Chronic Fatigue Syndrome was also reported more commonly among Dippers (OR 2.74; 95% CI 1.04-7.25), as was recurring general ill health (OR 2.76; 95% CI 1.56-4.91) and infection with the locally prevalent arboviruses Ross River Virus or Barmah Forest Virus (OR 2.17; 95% CI 1.23-3.85).

Table 4-9 Odds ratios for self reported outcomes by group

Outcome	Odds ratio	Lower Confidence Limit	Upper Confidence Limit	P Value
Asthma	**1.59**	**1.05**	**2.43**	**0.03**
Child With Asthma	**1.45**	**1.01**	**2.09**	**0.05**
Hay fever	0.98	0.67	1.45	0.94
Eczema/Dermatitis	**1.62**	**1.02**	**2.56**	**0.04**
Bronchitis	1.32	0.87	2.01	0.19
Emphysema	1.99	0.80	4.93	0.14
Skin Cancer	0.86	0.64	1.16	0.33
Depressed	1.22	0.73	2.05	0.45
Birth defect	1.01	0.53	1.92	0.97
Difficulty Achieving Pregnancy	1.37	0.72	2.61	0.33
Miscarriage	1.40	0.98	2.00	0.07
Any Children	0.82	0.56	1.21	0.33
Recurring Ill Health	**2.73**	**1.54**	**4.84**	**0.00**
Chronic Fatigue Syndrome	**2.66**	**1.01**	**7.02**	**0.05**
Diabetes	1.13	0.59	2.16	0.71
Arboviral infection	**2.14**	**1.21**	**3.78**	**0.01**
Heart Attack	0.99	0.59	1.66	0.97
Stroke	0.87	0.41	1.86	0.73
Circulatory Disease	1.23	0.86	1.75	0.26
Amputation	0.55	0.09	3.58	0.53
Other Heart	1.25	0.70	2.22	0.45
Parkinson's Disease	3.30	0.28	38.94	0.34
Long or Short Sighted	0.98	0.68	1.41	0.92
Epilepsy	5.01	0.51	49.38	0.17
Tingling or weakness in legs	1.23	0.80	1.89	0.35
Kidney	0.84	0.33	2.15	0.72
Hepatitis	0.84	0.44	1.61	0.59
Back	0.90	0.67	1.20	0.47
Fracture	1.00	0.60	1.68	0.99
Injury	1.18	0.87	1.60	0.28

Note: Logistic regression by group (Dipper or control) adjusted for log age, ever smoked

Since herbicides were by far the most frequently used chemical, and since their use was spread relatively evenly across both subcohorts, responses for different outcomes were also compared for subjects who had or had not used herbicides (Table 4-10).

Table 4-10 Odds ratios of outcomes by self reported occupational herbicide use

	ODDS RATIO	Lower Confidence Limit	Upper Confidence Limit	P VALUE
Asthma	1.31	0.86	2.01	0.21
Child With Asthma	1.25	0.87	1.79	0.24
Hay Fever	**1.82**	**1.23**	**2.69**	**0.00**
Eczema/Dermatitis	1.07	0.68	1.69	0.77
Bronchitis	1.27	0.84	1.93	0.26
Emphysema	0.99	0.41	2.39	0.99
Skin Cancer	1.20	0.90	1.61	0.21
Depressed	1.32	0.78	2.22	0.29
Birth Defect	1.51	0.79	2.86	0.21
Difficulty Achieving Pregnancy	0.57	0.30	1.09	0.09
Miscarriage	1.30	0.91	1.86	0.15
Any Children	1.26	0.86	1.85	0.24
Recurring Ill Health	1.70	0.95	3.03	0.07
Chronic Fatigue Syndrome	2.26	0.79	6.48	0.13
Diabetes	**2.26**	**1.15**	**4.43**	**0.02**
Arboviral Disease	0.97	0.55	1.72	0.93
Heart Attack	0.98	0.59	1.64	0.94
Stroke	**2.18**	**1.02**	**4.68**	**0.04**
Circulatory Disease	1.23	0.86	1.76	0.26
Amputation	2.96	0.45	19.31	0.26
Other Heart	1.02	0.58	1.82	0.94
Parkinson's Disease	0.67	0.06	7.69	0.75
Eyes	0.86	0.60	1.22	0.39
Epilepsy	2.59	0.26	25.56	0.42
Parasthesiae	1.27	0.83	1.96	0.28
Kidney	1.52	0.60	3.82	0.37
Hepatitis	1.27	0.68	2.40	0.45
Back	**1.45**	**1.09**	**1.93**	**0.01**
Fracture	**1.87**	**1.10**	**3.19**	**0.02**
Injury	1.29	0.96	1.73	0.10

Note: Logistic regression by herbicide exposure adjusted for log age, ever smoked

Subjects were also asked to complete a screening neuropsychological questionnaire comprising 16 questions. The yes/no answers to these were added to give a total score. Analysis of variance was undertaken to compare the total score between Dippers and controls.

Figure 4-4 illustrates the distribution of scores, which ranged from 0 (least neuropsychological problems) to 16 (more neuropsychological problems). The relationship of subject group with the logarithm of this score + 1 was explored using analysis of variance techniques.

Responding Dippers had a significantly higher log score +1 than controls after adjusting for age, indicating worse neuropsychological status (Table 4-11).

Figure 4-4 Range of neuropsychological scores in responding subjects

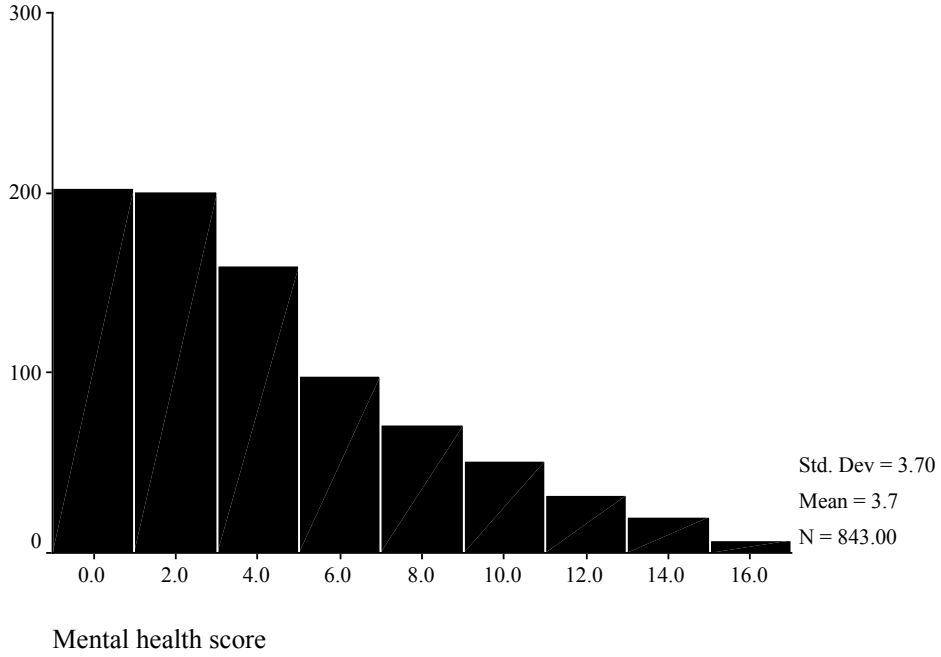


Table 4-11 Analysis of variance of relationship between ln neuropsychological score + 1 and group adjusted for age.

Tests of Between-Subjects Effects

Dependent Variable: LN(mental health score + 1)

Source	Type I Sum of Squares	df	Mean Square	F	Sig.
Corrected Model	7.717[a]	2	3.858	5.246	.005
Intercept	1196.417	1	1196.417	1626.629	.000
AGE	2.706	1	2.706	3.679	.055
GRP	5.011	1	5.011	6.812	.009
Error	589.886	802	.736		
Total	1794.020	805			
Corrected Total	597.603	804			

a. R Squared = .013 (Adjusted R Squared = .010)

4.3 MORTALITY

As described in the Methods section, the matching process comprised two phases. For the period 1980 to 1996, the cohort was matched against the National Deaths Index, while for the period 1945-1980, hand searches were made of the NSW and Queensland Deaths Registers. Since registries in other states were not searched for this earlier period, there is an inherent bias to underestimate deaths in the study population. However, during the later period when all Australian registries were searched using the National Deaths Index, the vast majority of deaths identified were recorded in either NSW or Queensland, suggesting this effect would be small. A total 691 deaths were identified for the period 1980-1996 from matching with the National Deaths Index (Table 4-12). Only 13 (2.0%) of these were recorded from states other than NSW or Queensland. If this proportion was consistent for earlier years (while in fact it may well have been lower due to less interstate migration) an additional 9 deaths would have been unidentified. 474 deaths for this period were identified from NSW and Queensland Registries. Dates of death ranged from 28 Nov 1945 to 13 December 1995.

Table 4-12 Origin of Death Notifications

	1945-1996		1945-1980		1980-1996	
State of Notification	Frequency	Percent	Frequency	Percent	Frequency	Percent
ACT	2	0.2			2	0.3
NSW	930	79.8	419	88.4	512	74.1
QLD	187	16.1	55	11.6	132	19.1
SA	3	0.3			2	0.3
TAS	3	0.3			3	0.4
VIC	3	0.3			3	0.4
WA	3	0.3			3	0.4
Missing	34	2.9			34	4.9
Total	1165		474		691	

4.3.1 Causes of Death

The 3983 subjects were followed for a total of over 82,000 person years of follow-up. An underlying cause of death was identified as described in the Methods section using the International Classification of Disease version 9. The exact number of deaths included (and reported) in each analysis varied with the restrictions placed on the model being used. For the general default model (termination of employment after 1934, deaths after 1944 and before 1996, either start or finish date of employment known) matching against the national and state death registries identified a total of 1080 deaths. Note that this includes deaths among controls not yet past the 10 year exposure lag and so does not correspond exactly with the observed deaths identified in output from SMR analysis. These results are summarised in (Table 4-13, Table 4-14, Table 4-15). Of the 1080 deaths identified, 366 were from ischaemic heart disease, 263 from cancer, 108 from respiratory disease and 79 from injury or poisoning.

Table 4-13 Deaths from main causes other than cancer

Underlying Cause of Death (ICD9)	Diagnosis	Freq	Percent of All Deaths	Dippers	Controls
ALL	All causes	1080	100	692	388
250	Diabetes	14	1.3	12	2
250.8		1	0.1	1	
410-414	IHD	366	33.9	232	134
390-459	All circulatory	540	50.0	346	194
492	Emphysema	12	1.1	6	6
493	Asthma	9	0.9	7	2
460-519	Respiratory	108	10.0	75	33
800-999	Injury and poisoning	79	7.3	48	31

Table 4-14 Deaths from cancer

Underlying Cause of Death (ICD9)	Diagnosis	Freq	Percent of All Deaths	Dippers	Controls
	ALL Cancer	263	23.4	168	95
38.9		1	0.1		1
136.0		1	0.1	1	
140.9		1	0.1		1
141.0		3	0.3	1	2
142.0		2	0.2	2	
146.0		2	0.2	1	1
146.9		1	0.1	1	
149.0		1	0.1	1	
150.0		3	0.3	2	1
150.9		3	0.3	2	1
151.0	Stomach	6	0.5	4	2
151.9		11	1.0	9	2
153.0	Colon	8	0.7	2	5
153.8		3	0.3	1	1
153.9		5	0.5	3	2
154.0	Rectum	4	0.4	3	1
154.1		7	0.6	5	2
155.0		4	0.4	1	3
157.0	Pancreas	7	0.6	5	2
157.9		4	0.4	4	

Table 4-15 Deaths from cancer (cont)

Underlying Cause of Death (ICD9)	Diagnosis	Freq	Percent of All Deaths	Dippers	Controls
159		1	0.1	1	
161.0		2	0.2	1	1
161.9		2	0.2	2	
162	Lung	44	4.1	31	13
162.1		6	0.5	4	2
162.9		35	3.2	21	14
170.0		3	0.3	2	1
171.5		1	0.1		1
172	Melanoma	7	0.6	3	4
172.6		1	0.1	1	
172.9		2	0.2	2	
173.0		3	0.3		3
173.8		1	0.1		1
173.9		1	0.1		1
185	Prostate	10	0.9	8	1
185.9		16	1.5	8	8
188.0	Bladder	5	0.5	2	3
188.9		4	0.4	3	1
189.0		3	0.3	3	
191.0	Brain	1	0.1		1
191.9		5	0.5	5	
195.9		1	0.1	1	
197.0		1	0.1		1
199.0	Not other specified	9	0.9	5	4
199.1		2	0.2	1	
200.0	Lympho-	2	0.2	2	
200.1	sarcoma	2	0.2	2	
201.9	Hodgkin's Disease	1	0.1	1	
202.0	Other	2	0.2	2	
202.8	Lymphoma	1	0.1		1
203.0	Multiple Myeloma	2	0.2	1	1
204.0	Lymphocytic leukaemia	4	0.4	2	2
205.0	Myeloid leukaemia	9	0.9	5	4
205.9		1	0.1	1	

4.3.2 Standardised Mortality Ratios

Standardised mortality ratios (SMRs) were estimated for all and specific causes of death for different cohort subgroups. SMRs were calculated using person years analysis comparing both exposed and control subgroups with the Australian population.

To explore the influence of exposure dose on outcomes, where information was available on dates of completion and termination of employment, the exposed subgroups were also categorised into groups depending on their duration of employment. Dippers were generally categorised into 4 groups outlined in Table 4-16. For Dippers working during the shorter DDT period from 1955-62, groupings were restricted to those working up to 3 years and those working 3 years or more.

Table 4-16 Criteria for exposure categorisation

Exposure Group	Definition
0	Dippers who had not yet completed 10 years of follow-up after entry to the study
1	Dippers working for less than 5 years
2	Dippers working for 5 or more years but less than 15 years
3	Dippers working for 15 or more years

As described in the Methods section, a range of models was used for analysis. The default model followed all subjects from 1935 to 1995 inclusive, incorporating an exposure lag period of 10 years. Where categories were defined by duration of employment (i.e. using the dose groups described above) all subjects for whom complete information on duration of employment was not available were excluded. However, information on duration of employment was not necessary to calculate overall SMRs for Dippers and controls during the total study period, or for subjects commencing work in the modern chemical periods (after 1963). To ensure the optimal use of information on the cohort, for these analyses only subjects with unknown dates of commencement were excluded. It should be noted that variations such as these in exclusion criteria result in minor differences in mortality estimates for the same outcome in different tables.

For some outcomes, the influence of different lag periods on SMR was also modeled.

The results of SMR analysis comparing both Dippers as a group and controls with the Australian population are summarised in Table 4-17 and Table 4-18.

Over the study period as a whole, all cause mortality was significantly increased amongst Dippers when compared as a group to the general Australian community (SMR 1.10; 95% CI 1.01-1.19). There was a similar statistically significant increase in mortality among controls (SMR 1.15; 95% CI 1.03-1.28).

Both Dippers and controls also showed increased mortality rates for a number of specific conditions. Dippers as a group had significantly increased mortality from asthma (SMR 2.92; 95% CI 1.17-6.01), ischaemic heart disease (SMR 1.39; 95% CI 1.21-1.60) and respiratory disease (SMR 1.59; 95% CI 1.25-2.01). Controls had statistically significant increases in mortality for circulatory disease (SMR 1.20; 95% CI 1.02-1.39), ischaemic heart disease (SMR 1.41; 95% CI 1.16-1.69) and respiratory disease (SMR 1.49; 95% CI 1.03-2.10). Dippers not yet having passed the 10-year exposure lag also had a statistically significant increase in mortality from ischaemic heart disease (SMR 2.37; 95% CI 1.56-3.45).

These disease patterns generally continued when analysis was limited to the modern (1962-96) chemical era (Table 4-19 and Table 4-20). Dippers as a group had statistically significant increases in mortality from all causes (SMR 1.34; 95% CI 1.13-1.58), asthma (SMR 5.62; 95% CI 1.16-16.43), circulatory disease (SMR 1.31; 95% CI 1.01-1.67) ischaemic heart disease (SMR 1.44; 95% CI 1.06-1.91) and respiratory disease (SMR 1.92; 95% CI 1.10-3.11). Over this period, controls also had similar statistically significantly increased mortality from all causes (SMR 1.39; 95% CI 1.16-1.64), circulatory disease (SMR 1.40; 95% CI 1.07-1.81) and ischaemic heart disease (SMR 1.43; 95% CI 1.03-1.93). Controls also had statistically significant increase in all cancer mortality over this period (SMR 1.53; 95% CI 1.10-2.06).

The earlier period of modern chemical use (1963-1976) showed similar patterns of mortality, although there were also statistically significant increases in mortality from diabetes among

Dippers (SMR 3.08; 95% CI 1.00-7.20), and lung cancer among controls (SMR 1.87; 95% CI 1.02-3.13). The ten year exposure lag and short follow-up made analysis of mortality during the later portion of the modern chemical era uninformative due to very small numbers of deaths (total 4 deaths observed).

When mortality was examined by duration of exposure, there were statistically significant increases in mortality ratios for a number of exposure groups (Table 4-21,Table 4-22, Table 4-23). Note that these results may vary slightly from Tables 4-16 to 4-19 since only subjects with full employment history were included in analysis. Mortality was significantly increased from all causes amongst Dippers working for more than 15 years in the total study period (SMR 1.19; 95% CI 1.04-1.35) and for between 5 and 15 years in the modern chemical period (SMR 1.39, 95% CI 1.07-1,77). Other significant increases in mortality among Dippers were from asthma in Dippers working between 5 and 15 years in the modern chemical period (SMR 9.31; 95% CI 1.13-33.62), and from diabetes among Dippers working less than 5 years overall (SMR 3.57, 1.16-8.32). Deaths from ischaemic heart disease and respiratory disease were also more common in a range of exposure groups.

The only form of cancer with mortality significantly more common than in the general Australian population was pancreatic cancer among Dippers working less than 3 years during the period of DDT use (SMR 5.27; 95% CI 1.09-15.40).

Table 4-17 Standardised Mortality Ratios adjusted for age and period of followup.

	All Chemical Periods (1935-95)				
Dose	EXP	OBS	SMR	LCI	UCI
ALL DEATHS					
Dose 0	84.01	85	1.01	0.81	1.25
All Exposed	552.84	607	**1.10**	**1.01**	**1.19**
Controls	287.20	331	**1.15**	**1.03**	**1.28**
ASTHMA					
Dose 0	0.50	0	0.00	0.00	5.99
All Exposed	2.40	7	**2.92**	**1.17**	**6.01**
Controls	1.37	2	1.46	0.18	5.27
CIRCULATORY DISEASE					
Dose 0	35.74	37	1.04	0.73	1.43
All Exposed	280.38	309	1.10	0.98	1.23
Controls	138.01	165	**1.20**	**1.02**	**1.39**
DIABETES					
Dose 0	0.80	1	1.25	0.03	6.95
All Exposed	7.95	12	1.51	0.78	2.64
Controls	4.19	2	0.48	0.06	1.72
EMPHYSEMA					
Dose 0	0.33	0	0.00	0.00	9.22
All Exposed	4.62	6	1.30	0.48	2.82
Controls	2.39	6	2.51	0.92	5.46
ISCHAEMIC HEART DISEASE					
Dose 0	11.38	27	**2.37**	**1.56**	**3.45**
All Exposed	147.10	205	**1.39**	**1.21**	**1.60**
Controls	81.70	115	**1.41**	**1.16**	**1.69**
RESPIRATORY DISEASE					
Dose 0	4.48	3	0.67	0.14	1.96
All Exposed	45.17	72	**1.59**	**1.25**	**2.01**
Controls	22.11	33	**1.49**	**1.03**	**2.10**
ALL CANCERS					
Dose 0	15.01	20	1.33	0.81	2.06
All Exposed	127.06	148	1.16	0.98	1.37
Controls	72.06	85	1.18	0.94	1.46

Note: Indirect standardisation to Australian population, person years analysis, confidence intervals determined by Poisson regression. 10 year exposure lag. Dose 0 relates to exposed subjects not yet past 10 year exposure lag. Controls not yet followed for 10 years excluded. Significant results highlighted.

Table 4-18 Standardised Mortality Ratios adjusted for age and period of followup.

	All Chemical Periods (1935-95)				
Dose	EXP	OBS	SMR	LCI	UCI
BLADDER CANCER					
Dose 0	0.30	2	6.62	0.80	23.91
All Exposed	3.73	3	0.80	0.17	2.35
Controls	1.89	4	2.12	0.58	5.42
BRAIN CANCER					
Dose 0	0.73	2	2.73	0.33	9.87
All Exposed	3.30	3	0.91	0.19	2.65
Controls	2.22	1	0.45	0.01	2.51
COLON CANCER					
Dose 0	1.28	0	0.00	0.00	2.34
All Exposed	11.23	6	0.53	0.20	1.16
Controls	6.40	7	1.09	0.44	2.25
LEUKAEMIA (All Types)					
Dose 0	0.67	1	1.49	0.04	8.29
All Exposed	3.95	7	1.77	0.71	3.65
Controls	2.27	4	1.76	0.48	4.50
LUNG CANCER					
Dose 0	3.96	7	1.77	0.71	3.64
All Exposed	37.24	49	1.32	0.97	1.74
Controls	21.41	26	1.21	0.79	1.78
NON HODGKINS LYMPHOMA					
Dose 0	0.52	0	0.00	0.00	5.72
All Exposed	3.66	6	1.64	0.60	3.57
Controls	2.24	1	0.45	0.01	2.49
PANCREATIC CANCER					
Cancer Dose 0	0.72	1	1.40	0.04	7.78
All Exposed	5.86	8	1.36	0.59	2.69
Controls	3.30	2	0.61	0.07	2.19
PROSTATE CANCER					
Dose 0	0.39	0	0.00	0.00	7.67
All Exposed	12.11	16	1.32	0.76	2.15
Controls	6.06	8	1.32	0.57	2.60
RECTAL CANCER					
Dose 0	0.58	0	0.00	0.00	5.13
All Exposed	4.94	8	1.62	0.70	3.19
Controls	2.78	3	1.08	0.22	3.15
STOMACH CANCER					
Dose 0	1.39	2	1.44	0.17	5.21
All Exposed	9.11	11	1.21	0.60	2.16
Controls	4.52	3	0.66	0.14	1.94

Note: Indirect standardisation to Australian population, person years analysis, confidence intervals determined by Poisson regression. 10 year exposure lag. Dose 0 relates to exposed subjects not yet past 10 year exposure lag. Controls not yet followed for 10 years excluded. Significant results highlighted.

Table 4-19 Standardised Mortality Ratios for subjects working during the period of modern chemicals adjusted for age and period of follow-up

	Early Modern Chemical Period (1963-76)					Total Modern Chemical Period (1963-95)				
Dose	EXP	OBS	SMR	LCI	UCI	EXP	OBS	SMR	LCI	UCI
ALL DEATHS										
Dose 0	57.89	67	1.16	0.90	1.47	54.95	61	1.11	0.85	1.43
All Exposed	104.32	138	**1.32**	**1.11**	**1.56**	107.26	144	**1.34**	**1.13**	**1.58**
Controls	89.91	125	**1.39**	**1.16**	**1.66**	97.44	135	**1.39**	**1.16**	**1.64**
ASTHMA										
Dose 0	0.34	0	0.00	0.00	8.92	0.32	0	0.00	0.00	9.42
All Exposed	0.52	3	**5.82**	**1.20**	**17.00**	0.53	3	**5.62**	**1.16**	**16.43**
Controls	0.47	1	2.11	0.05	11.78	0.52	1	1.92	0.05	10.69
CIRCULATORY DISEASE										
Dose 0	25.10	34	1.35	0.94	1.89	24.13	29	1.20	0.81	1.73
All Exposed	48.02	59	1.23	0.94	1.59	48.99	64	**1.31**	**1.01**	**1.67**
Controls	40.34	58	**1.44**	**1.09**	**1.86**	42.74	60	**1.40**	**1.07**	**1.81**
DIABETES										
Dose 0	0.63	1	1.58	0.04	8.79	0.59	1	1.70	0.04	9.47
All Exposed	1.62	5	**3.08**	**1.00**	**7.20**	1.67	5	3.00	0.97	7.00
Controls	1.36	1	0.74	0.02	4.10	1.47	1	0.68	0.02	3.80
EMPHYSEMA										
Dose 0	0.28	0	0.00	0.00	10.75	0.26	0	0.00	0.00	11.53
All Exposed	0.96	3	3.13	0.65	9.14	0.98	3	3.07	0.63	8.97
Controls	0.76	2	2.63	0.32	9.51	0.80	2	2.50	0.30	9.01
ISCHAEMIC HEART DISEASE										
Dose 0	13.96	24	**1.72**	**1.10**	**2.56**	13.30	21	1.58	0.98	2.41
All Exposed	32.72	45	**1.38**	**1.00**	**1.84**	33.38	48	**1.44**	**1.06**	**1.91**
Controls	27.71	41	**1.48**	**1.06**	**2.01**	29.39	42	**1.43**	**1.03**	**1.93**
RESPIRATORY DISEASE										
Dose 0	3.08	1	0.33	0.00	1.81	2.91	1	0.34	0.00	1.91
All Exposed	8.18	16	**1.96**	**1.12**	**3.18**	8.35	16	**1.92**	**1.10**	**3.11**
Controls	6.58	12	1.82	0.94	3.18	6.95	12	1.73	0.89	3.02
ALL CANCERS										
Dose 0	11.78	13	1.10	0.59	1.89	10.91	12	1.10	0.57	1.92
All Exposed	29.00	39	1.34	0.96	1.84	29.87	40	1.34	0.96	1.82
Controls	25.24	37	**1.47**	**1.03**	**2.02**	27.50	42	**1.53**	**1.10**	**2.06**

Note: Indirect standardisation to Australian population, person years analysis, confidence intervals determined by Poisson regression. 10 year exposure lag. Dose 0 relates to exposed subjects not yet past 10 year exposure lag. Controls not yet followed for 10 years excluded. Significant results highlighted.

Table 4-20 Standardised Mortality Ratios for cancers in subjects working during the period of modern chemicals adjusted for age and period of follow-up

	Early Modern Chemical Period (1963-76)					Total Modern Chemical Period (1963-95)				
Dose	EXP	OBS	SMR	LCI	UCI	EXP	OBS	SMR	LCI	UCI
BLADDER CANCER										
Dose 0	0.23	0	0.00	0.00	13.19	0.21	0	0.00	0.00	14.18
All Exposed	0.73	0	0.00	0.00	4.08	0.75	0	0.00	0.00	3.99
Controls	0.59	0	0.00	0.00	5.07	0.63	0	0.00	0.00	4.79
BRAIN CANCER										
Dose 0	0.59	2	3.41	0.41	12.32	0.55	2	3.67	0.44	13.25
All Exposed	0.88	2	2.27	0.28	8.21	0.92	2	2.17	0.26	7.84
Controls	0.86	0	0.00	0.00	3.46	0.98	1	1.02	0.03	5.66
COLON CANCER										
Dose 0	1.00	0	0.00	0.00	2.99	0.92	0	0.00	0.00	3.24
All Exposed	2.59	3	1.16	0.24	3.38	2.67	3	1.12	0.23	3.28
Controls	2.28	4	1.75	0.48	4.48	2.49	4	1.60	0.44	4.11
LEUKAEMIA (All Types)										
Dose 0	1.04	3	2.87	0.59	8.39	0.45	1	2.21	0.06	12.31
All Exposed	0.33	1	3.00	0.08	16.73	0.92	3	3.24	0.67	9.48
Controls	0.29	0	0.00	0.00	10.25	0.88	2	2.28	0.28	8.23
LUNG CANCER										
Dose 0	3.47	3	0.87	0.18	2.53	3.24	3	0.93	0.19	2.71
All Exposed	8.73	14	1.60	0.88	2.69	8.96	14	1.56	0.85	2.62
Controls	7.50	14	**1.87**	**1.02**	**3.13**	8.08	14	1.73	0.95	2.91
NON HODGKINS LYMPHOMA										
Dose 0	1.02	1	0.98	0.02	5.44	0.39	0	0.00	0.00	7.68
All Exposed	0.32	0	0.00	0.00	9.23	0.96	1	1.04	0.03	5.81
Controls	0.28	0	0.00	0.00	10.71	0.94	0	0.00	0.00	3.19
PANCREATIC CANCER										
Cancer Dose 0	0.58	1	1.74	0.04	9.67	0.54	1	1.85	0.05	10.33
All Exposed	1.30	0	0.00	0.00	2.31	1.33	0	0.00	0.00	2.24
Controls	1.14	1	0.88	0.02	4.90					
PROSTATE CANCER										
Dose 0	0.36	0	0.00	0.00	8.38	0.30	0	0.00	0.00	10.01
All Exposed	2.54	4	1.57	0.43	4.03	2.60	4	1.54	0.42	3.94
Controls	1.95	3	1.54	0.32	4.50	1.23	1	0.81	0.02	4.52
RECTAL CANCER										
Dose 0	0.44	0	0.00	0.00	6.76	0.41	0	0.00	0.00	7.32
All Exposed	1.11	1	0.90	0.02	5.03	1.14	1	0.88	0.02	4.88
Controls	0.98	1	1.02	0.03	5.70	1.07	2	1.87	0.23	6.76
STOMACH CANCER										
Dose 0	0.83	1	1.21	0.03	6.75	0.79	1	1.27	0.03	7.07
All Exposed	1.58	3	1.90	0.39	5.55	1.62	3	1.85	0.38	5.42
Controls	1.36	1	0.74	0.02	4.10	1.46	1	0.69	0.02	3.82

Note: Indirect standardisation to Australian population, person years analysis, confidence intervals determined by Poisson regression. 10 year exposure lag. Dose 0 relates to exposed subjects not yet past 10 year exposure lag. Controls not yet followed for 10 years excluded. Significant results highlighted.

Table 4-21 Standardised Mortality Ratios for Dippers and Controls by exposure group adjusted for age and period of follow-up

	All Chemical Periods			Arsenic Period			DDT Period			Modern Chemical Period		
Exposure Group	SMR	LCI	UCI	SMR	LCI	UCI	SMR	LCI	UCI	SMR	LCI	UCI
All Deaths												
Controls	1.08	0.96	1.22	1.00	0.81	1.23	1.07	0.92	1.24	**1.24**	**1.01**	**1.50**
All	**1.10**	**1.01**	**1.20**	0.97	0.83	1.12	1.09	0.98	1.20	**1.28**	**1.06**	**1.53**
Dose 0	1.00	0.78	1.26							1.06	0.79	1.40
Dose 1	1.03	0.84	1.24	1.00	0.75	1.30	1.03	0.78	1.33	1.09	0.81	1.44
Dose 2	1.04	0.90	1.21	0.80	0.60	1.04	1.10	0.98	1.23	**1.39**	**1.07**	**1.77**
Dose 3	**1.19**	**1.04**	**1.35**	1.16	0.89	1.49				2.13	0.97	4.04
Asthma												
Controls	1.61	0.19	5.81	0.00	0.00	7.48	1.40	0.04	7.81	2.22	0.06	12.37
All	**3.45**	**1.39**	**7.10**	3.94	0.81	11.51	2.27	0.47	6.64	**6.44**	**1.33**	**18.82**
Dose 0	0.00	0.00	7.05							0.00	0.00	11.00
Dose 1	3.87	0.47	14.00	3.61	0.09	20.09	0.00	0.00	12.11	4.36	0.11	24.31
Dose 2	3.89	0.80	11.38	6.09	0.74	21.99	2.80	0.58	8.17	**9.31**	**1.13**	**33.62**
Dose 3	2.69	0.33	9.71	0.00	0.00	19.23				0.00	0.00	136.9
Circulatory Disease												
Controls	1.11	0.94	1.31	1.07	0.80	1.41	1.11	0.90	1.36	1.19	0.87	1.59
All	1.08	0.95	1.23	0.93	0.75	1.15	1.09	0.94	1.25	1.13	0.83	1.49
Dose 0	1.00	0.68	1.42							1.17	0.75	1.72
Dose 1	1.11	0.83	1.45	0.72	0.44	1.11	1.10	0.75	1.56	1.11	0.71	1.67
Dose 2	1.03	0.83	1.27	0.83	0.56	1.18	1.06	0.92	1.27	1.22	0.86	1.79
Dose 3	1.12	0.92	1.34	1.26	0.89	1.74				1.74	0.36	5.08
Diabetes												
Controls	0.52	0.06	1.87	0.85	0.02	4.73	0.40	0.01	2.21	0.77	0.02	4.31
All	1.49	0.71	2.74	0.85	0.02	4.73	1.22	0.45	2.65	2.70	0.74	6.91
Dose 0	1.45	0.04	8.06							1.93	0.05	10.76
Dose 1	**3.57**	**1.16**	**8.32**	1.47	0.04	8.18	1.30	0.03	7.26	2.96	0.36	10.71
Dose 2	1.66	0.45	4.26	0.00	0.00	3.43	1.20	0.39	2.80	2.76	0.33	9.95
Dose 3	0.34	0.00	1.92	0.00	0.00	4.18				0.00	0.00	36.71
Emphysema												
Controls	2.69	0.99	5.85	2.89	0.35	10.45	2.67	0.73	6.83	2.78	0.34	10.06
All	1.53	0.56	3.32	0.77	0.02	4.28	1.02	0.21	2.99	3.41	0.70	9.97
Dose 0	0.00	0.00	10.55							0.00	0.00	13.00
Dose 1	2.63	0.32	9.49	2.66	0.07	14.81	0.00	0.00	7.06	5.16	0.63	18.65
Dose 2	0.70	0.02	3.91	0.00	0.00	5.89	1.20	0.25	3.50	2.23	0.06	12.42
Dose 3	1.72	0.35	5.02	0.00	0.00	7.21				0.00	0.00	69.27
Ischaemic Heart Disease												
Controls	**1.38**	**1.13**	**1.68**	**1.80**	**1.29**	**2.45**	**1.38**	**1.08**	**1.74**	1.31	0.91	1.83
All	**1.37**	**1.18**	**1.59**	**1.36**	**1.02**	**1.78**	**1.31**	**1.09**	**1.56**	1.28	0.91	1.76
Dose 0	**2.21**	**1.38**	**3.34**							1.53	0.91	2.42
Dose 1	**1.70**	**1.24**	**2.29**	0.85	0.44	1.48	**2.09**	**1.37**	**3.07**	1.32	0.79	2.06
Dose 2	1.25	0.95	1.62	1.56	0.98	2.37	1.20	0.98	1.45	1.14	0.65	1.85
Dose 3	**1.32**	**1.03**	**1.66**	**1.79**	**1.07**	**2.79**				2.55	0.53	7.46

Note: Indirect standardisation to Australian population, person years analysis, confidence intervals determined by Poisson regression. Subjects without full employment details excluded. 10 year exposure lag. Controls not yet followed for 10 years excluded. Significant results highlighted.

Dose indicates duration of exposure. Dose 0 relates to exposed subjects not yet past 10 year exposure lag. For all except the DDT period of chemical use, "All" equates to any employment during this period, "Dose1" equates to less than 5 years employment, "Dose2" equates to 5 or more but less than 15 years of employment and "Dose3" equates to more than 15 years employment. For the DDT period, "Dose1" represents less than 3 years and "Dose2" represents more than 3 years of employment.

Table 4-22 Standardised Mortality Ratios for Dippers and Controls by exposure group adjusted for age, period of follow-up

	All Chemical Periods			Arsenic Period			DDT Period			Modern Chemical Period		
Exposure Group	SMR	LCI	UCI	SMR	LCI	UCI	SMR	LCI	UCI	SMR	LCI	UCI
Respiratory Disease												
Controls	**1.50**	**1.02**	**2.12**	1.29	0.59	2.44	1.43	0.87	2.21	1.92	0.99	3.36
All	**1.61**	**1.24**	**2.07**	**1.72**	**1.10**	**2.55**	**1.60**	**1.16**	**2.13**	**1.87**	**1.02**	**3.14**
Dose 0	0.52	0.06	1.87							0.00	0.00	1.17
Dose 1	1.09	0.47	2.14	**2.36**	**1.08**	**4.49**	0.45	0.06	1.64	1.52	0.49	3.54
Dose 2	1.39	0.84	2.17	1.67	0.76	3.17	**1.81**	**1.31**	**2.43**	1.83	0.73	3.76
Dose 3	**2.03**	**1.41**	**2.84**	1.25	0.46	2.73				5.68	0.69	20.52
All Cancer												
Controls	1.07	0.83	1.35	1.01	0.61	1.57	1.01	0.73	1.38	1.30	0.88	1.84
All	1.18	0.99	1.41	1.01	0.70	1.40	1.15	0.92	1.42	1.29	0.89	1.80
Dose 0	1.24	0.71	2.01							0.94	0.43	1.79
Dose 1	1.06	0.69	1.56	1.16	0.64	1.95	1.07	0.57	1.83	1.21	0.68	1.99
Dose 2	1.12	0.81	1.51	0.66	0.30	1.26	1.16	0.92	1.46	1.20	0.67	1.97
Dose 3	1.30	0.99	1.68	1.31	0.68	2.29				2.75	0.75	7.03
Bladder Cancer												
Controls	2.27	0.62	5.82	1.84	0.05	10.23	3.41	0.93	8.74	0.00	0.00	5.37
All	0.96	0.20	2.80	0.00	0.00	2.78	1.30	0.27	3.79	0.00	0.00	4.45
Dose 0	7.67	0.93	27.70							0.00	0.00	15.94
Dose 1	0.00	0.00	4.86	0.00	0.00	10.04	0.00	0.00	8.32	0.00	0.00	10.24
Dose 2	0.89	0.02	4.94	0.00	0.00	7.11	1.54	0.32	4.49	0.00	0.00	8.64
Dose 3	1.44	0.17	5.19	0.00	0.00	8.39				0.00	0.00	86.91
Brain Cancer												
Controls	0.51	0.01	2.83	0.00	0.00	5.61	0.00	0.00	2.81	1.19	0.03	6.63
All	0.70	0.09	2.54	0.00	0.00	3.43	0.53	0.01	2.98	1.27	0.03	7.06
Dose 0	3.19	0.39	11.54							4.28	0.52	15.46
Dose 1	0.00	0.00	3.73	0.00	0.00	7.27	0.00	0.00	9.18	0.00	0.00	7.28
Dose 2	1.92	0.23	6.95	0.00	0.00	8.68	0.65	0.02	3.61	2.97	0.08	16.57
Dose 3	0.00	0.00	3.01	0.00	0.00	25.52				0.00	0.00	71.33
Colon Cancer												
Controls	1.03	0.38	2.25	0.00	0.00	5.61	0.85	0.17	2.47	1.39	0.29	4.07
All	0.63	0.23	1.37	0.66	0.08	2.38	0.45	0.09	1.30	1.27	0.26	3.72
Dose 0	0.00	0.00	2.72							0.00	0.00	3.71
Dose 1	0.00	0.00	1.38	0.96	0.02	5.34	0.00	0.00	2.83	0.00	0.00	2.70
Dose 2	0.59	0.07	2.14	0.85	0.02	4.73	0.53	0.11	1.54	1.79	0.22	6.46
Dose 3	1.00	0.27	2.56	0.00	0.00	3.70				7.55	0.19	42.08
Leukaemia (All Types)												
Controls	1.93	0.53	4.94	1.69	0.04	9.39	1.61	0.19	5.80	2.61	0.32	9.44
All	1.79	0.66	3.89	0.92	0.02	5.11	1.69	0.46	4.34	3.70	0.76	10.81
Dose 0	1.74	0.04	9.71	2.11	0.77	4.60	1.89	0.39	5.53	2.58	0.07	14.36
Dose 1	2.51	0.30	9.08	2.59	0.07	14.43	2.57	0.06	14.29	5.20	0.63	18.79
Dose 2	0.83	0.02	4.61	0.00	0.00	7.08	1.52	0.31	4.45	0.00	0.00	7.82
Dose 3	2.22	0.46	6.48	0.00	0.00	10.71				22.89	0.58	127.53

Note: Indirect standardisation to Australian population, person years analysis, confidence intervals determined by Poisson regression. Subjects without full employment details excluded. 10 year exposure lag. Controls not yet followed for 10 years excluded. Significant results highlighted.

Dose indicates duration of exposure. Dose 0 relates to exposed subjects not yet past 10 year exposure lag. For all except the DDT period of chemical use, "All" equates to any employment during this period, "Dose1" equates to less than 5 years employment, "Dose2" equates to 5 or more but less than 15 years of employment and "Dose3" equates to more than 15 years employment. For the DDT period, "Dose1" represents less than 3 years and "Dose2" represents more than 3 years of employment.

Table 4-23 Standardised Mortality Ratios for Dippers and Controls by exposure group adjusted for age, period of follow-up

	All Periods			Arsenic Period			DDT Period			Modern Chemical Period		
Exposure Group	SMR	LCI	UCI	SMR	LCI	UCI	SMR	LCI	UCI	SMR	LCI	UCI
Lung Cancer												
Controls	1.13	0.71	1.71	1.37	0.59	2.69	0.98	0.51	1.72	1.57	0.78	2.81
All	1.34	0.97	1.81	1.08	0.54	1.93	1.27	0.85	1.83	1.51	0.78	2.63
Dose 0	1.73	0.64	3.77							1.05	0.22	3.06
Dose 1	0.97	0.39	1.99	1.34	0.43	3.12	0.28	0.00	1.56	1.31	0.43	3.06
Dose 2	1.59	0.94	2.51	1.01	0.27	2.58	1.45	0.97	2.10	1.61	0.59	3.49
Dose 3	1.34	0.80	2.12	0.80	0.10	2.89				2.38	0.06	13.25
Non Hodgkin's Lymphoma												
Controls	0.50	0.01	2.76	0.00	0.00	5.88	0.85	0.02	4.75	0.00	0.00	3.70
All	1.60	0.52	3.73	2.20	0.27	7.96	1.84	0.50	4.72	1.19	0.03	6.66
Dose 0	0.00	0.00	6.67	1.12	0.23	3.28	0.70	0.02	3.90	0.00	0.00	8.91
Dose 1	0.00	0.00	3.91	2.84	0.07	15.83	0.00	0.00	8.54	0.00	0.00	7.48
Dose 2	1.81	0.22	6.52	2.87	0.07	15.99	2.20	0.60	5.63	2.58	0.07	14.37
Dose 3	2.38	0.49	6.97	0.00	0.00	14.44				0.00	0.00	61.12
Pancreatic Cancer												
Controls	0.67	0.08	2.41	0.00	0.00	3.25	0.54	0.01	2.99	0.94	0.02	5.22
All	1.61	0.69	3.16	1.78	0.37	5.19	1.98	0.79	4.07	0.00	0.00	2.53
Dose 0	0.00	0.00	4.82							0.00	0.00	6.28
Dose 1	0.88	0.02	4.91	3.39	0.41	12.23	**5.27**	**1.09**	**15.40**	0.00	0.00	5.26
Dose 2	1.12	0.14	4.05	0.00	0.00	4.51	1.35	0.37	3.44	0.00	0.00	5.45
Dose 3	2.43	0.79	5.66	2.30	0.06	12.83				0.00	0.00	47.70
Prostate Cancer												
Controls	1.23	0.50	2.54	1.44	0.17	5.22	1.30	0.42	3.04	1.62	0.33	4.72
All	1.48	0.83	2.43	1.73	0.56	4.03	1.17	0.54	2.23	1.70	0.46	4.36
Dose 0	0.00	0.00	8.85							0.00	0.00	11.31
Dose 1	2.75	0.89	6.42	1.57	0.04	8.76	1.77	0.21	6.40	2.18	0.26	7.89
Dose 2	0.85	0.18	2.49	0.00	0.00	2.78	1.07	0.43	2.21	1.56	0.19	5.64
Dose 3	1.45	0.58	2.99	3.38	0.92	8.66				0.00	0.00	19.59
Rectal Cancer												
Controls	0.79	0.10	2.86	0.00	0.00	4.00	0.65	0.02	3.60	1.08	0.03	6.03
All	1.43	0.53	3.12	2.14	0.44	6.26	1.70	0.55	3.97	0.99	0.03	5.52
Dose 0	0.00	0.00	5.96							0.00	0.00	8.33
Dose 1	1.06	0.03	5.89	2.11	0.05	11.75	0.00	0.00	6.44	2.09	0.05	11.64
Dose 2	1.34	0.16	4.83	1.80	0.05	10.03	2.02	0.66	4.71	0.00	0.00	6.29
Dose 3	1.72	0.36	5.03	2.70	0.07	15.06				0.00	0.00	55.86
Stomach Cancer												
Controls	0.24	0.00	1.33	0.00	0.00	1.85	0.38	0.00	2.09	0.00	0.00	2.34
All	1.19	0.54	2.26	0.92	0.19	2.69	1.32	0.53	2.73	1.39	0.17	5.04
Dose 0	1.69	0.20	6.09							1.43	0.04	7.97
Dose 1	1.21	0.15	4.36	1.03	0.03	5.74	2.22	0.27	8.00	1.44	0.04	8.02
Dose 2	1.41	0.38	3.60	0.73	0.02	4.09	1.14	0.37	2.66	1.48	0.04	8.26
Dose 3	0.98	0.20	2.85	1.08	0.03	6.01				0.00	0.00	46.89

Note: Indirect standardisation to Australian population, person years analysis, confidence intervals determined by Poisson regression. Subjects without full employment details excluded. 10 year exposure lag. Controls not yet followed for 10 years excluded. Significant results highlighted.

Dose indicates duration of exposure. Dose 0 relates to exposed subjects not yet past 10 year exposure lag. For all except the DDT period of chemical use, "All" equates to any employment during this period, "Dose1" equates to less than 5 years employment, "Dose2" equates to 5 or more but less than 15 years of employment and "Dose3" equates to more than 15 years employment. For the DDT period, "Dose1" represents less than 3 years and "Dose2" represents more than 3 years of employment.

4.3.3 Comparison of underlying cause of death between exposed and control subcohorts

As described in the Methods section, deaths in the exposed (Dipper) subcohort were also compared directly to deaths in the control (Council Worker) subcohort. Standardised Incidence Ratios (SIRs) were calculated using Poisson regression to compare death rates in the total exposed sub cohort with rates among controls, as well as for different exposure subgroups. Common outcomes with large numbers of deaths allowed both age at death (specifically the log of the midpoint of 10 year age groups) and the influence of changing death rates at different times during the follow up period (whether subjects worked before or after 1960) to be included in a multivariate Poisson analysis. This approach was used for total deaths, and for deaths from circulatory disease and ischaemic heart disease.

Because of limitations resulting from small numbers of events in the internal comparison, the multivariate Poisson regression model was limited to exposure subgroup and age for less common outcomes. For all outcomes, confidence intervals were calculated using maximum likelihood methods. Some causes of mortality had numbers too small in one or other group for the statistical analysis to be undertaken successfully.

As well as comparing mortality across the whole study period, where possible, mortality was also assessed for the same periods of chemical use and by the same exposure categories used in calculation of standardised mortality ratios.

Table 4-24 illustrates standardised incidence ratios calculated by this analysis for Dippers as a group compared to controls over the total study period and during the period of modern chemical use. There were no statistically significant differences in mortality between the two groups in either period. Conditions where the SMR was more than 2.5 over the total study period included asthma (SIR 2.96, 95% CI 0.59-14.91), diabetes (SIR 4.18; 95% CI 0.92-19.05), Non Hodgkin's lymphoma, brain cancer (SIR 3.13; 95% CI 0.29-33.43) and pancreatic cancer (SIR 2.72; 95% CI 0.56-13.12).

Table 4-24 Comparison of mortality between all exposed Dippers and Controls (includes subjects with incomplete employment data)

	Total Study period (1935-95)			Modern Chemical Period (1963-95)		
Condition	SIR	LCI	UCI	SIR	LCI	UCI
All deaths	1.09	0.96	1.25	1.10	0.88	1.38
Asthma	2.96	0.59	14.91	4.31	0.42	44.57
Circulatory Disease	1.07	0.89	1.28	0.97	0.70	1.35
Diabetes	4.18	0.92	19.05	5.59	0.63	49.87
Emphysema	0.54	0.17	1.69	-	-	-
IHD	1.06	0.85	1.32	1.03	0.70	1.52
Respiratory Disease	1.22	0.81	1.86	1.32	0.62	2.84
All Cancers	1.12	0.86	1.46	1.17	0.77	1.79
Bladder Cancer	0.40	0.09	1.84	-	-	-
Brain Cancer	3.13	0.29	33.43	1.82	0.23	14.10
Colon Cancer	0.52	0.18	1.54	0.87	0.20	3.84
Hodgkin's Disease	-	-	-	-	-	-
Lung Cancer	1.15	0.72	1.83	0.99	0.49	2.03
Lymphocytic Leukaemia	1.39	0.17	11.54	6.81	0.30	156.85
Melanoma	0.62	0.10	3.72	0.68	0.07	6.60
Multiple Myeloma	0.59	0.04	9.87	-	-	-
Myeloid Leukaemia	1.09	0.28	4.29	1.36	0.21	8.80
NHL	4.57	0.53	39.39	-	-	-
Other Skin	-	-	-	-	-	-
Pancreatic Cancer	2.72	0.56	13.12	-	-	-
Prostate Cancer	1.05	0.46	2.39	0.98	0.24	4.05
Rectal Cancer	2.02	0.52	7.86	0.63	0.05	7.40
Stomach Cancer	2.12	0.66	6.87	3.04	0.47	19.82

Note: For all deaths, circulatory disease, and ischaemic heart disease (IHD) during the total study period the Poisson regression model included log age and whether the year of death occurred before or after 1960. For all other outcomes model included log age. Likelihood ratio confidence limits, 10 year exposure lag. Significant results highlighted. – denotes failure to converge.

The results of analysis by exposure category and period of chemical use is shown in Table 4-25, Table 4-26 and Table 4-27. It should again be noted that these results vary from Table 4-23 since subjects without full employment history are excluded. Where statistical convergence could not be attained due to small numbers, these cells are identified in the table.

Over the whole study period, there was a small excess of total deaths amongst Dippers when compared with controls (SIR 1.13; 95% CI 0.98-1.30). This was statistically significant for subjects working more than 15 years (SIR 1.25; 95% CI 1.05-1.49), and there was a dose response gradient (Dose1 SIR 0.96, Dose2 SIR 1.12, Dose3 SIR 1.25). Total mortality was significantly increased for Dippers working during the period of DDT use (SIR 1.17; 95% CI 1.01-1.36) and for Dippers working in the maximum exposure groups for DDT (SIR 1.18; 95% CI 1.01-1.38) and for arsenic (SIR 1.53; 95% CI 1.16-2.02).

When Dippers working through the total study period were assessed by exposure, mortality from Diabetes in the less than 5 years exposure group was significantly increased (SIR 7.68; 95% CI 1.49-39.61), as was mortality from total cancers (SIR 1.49; 95% CI 1.05-2.13).

For the arsenic period (subjects working before 1955), Dippers working for more than 15 years had a significantly increased mortality from circulatory disease (SIR 1.53; 95% CI 1.27-2.60). No other specific causes of death were significantly more common in workers from this period.

During the DDT period, mortality from pancreatic cancer was significantly increased in Dippers working less than 3 years (SIR 7.0; 95% CI 1.39-35.32).

Dippers working over 15 years through the modern chemical period (1962 onwards) had a significantly increased mortality from myeloid leukaemia (SIR 20.90; 95% CI 1.54-284.41). Analysis by early and late portions of the modern chemical period was generally not possible due to small numbers of deaths.

Table 4-25 Comparison of mortality in Dippers and Controls by exposure group (for subjects with complete employment data).

	All Chemical Periods (1935-95)			Arsenic Period (1935-55)			DDT Period (1955-62)			Modern Chemicals Period (1963-95)		
Dose	SIR	LCI	UCI	SIR	LCI	UCI	SIR	LCI	UCI	SIR	LCI	UCI
All deaths												
All	1.13	0.98	1.30	1.11	0.94	1.32	**1.17**	**1.01**	**1.36**	1.14	0.89	1.45
Dose1	0.96	0.77	1.20	1.07	0.85	1.35	1.10	0.83	1.45	0.93	0.67	1.28
Dose2	1.12	0.93	1.35	0.96	0.74	1.23	**1.18**	**1.01**	**1.38**	1.34	0.98	1.81
Dose3	**1.25**	**1.05**	**1.49**	**1.53**	**1.16**	**2.02**				1.65	0.84	3.25
Asthma												
All	3.09	0.62	15.52	2.79	0.44	17.72	1.62	0.30	8.85	4.38	0.42	45.78
Dose1	3.16	0.44	22.45	-	-	-	-	-	-	3.05	0.18	50.38
Dose2	3.53	0.57	21.81	-	-	-	-	-	-	6.71	0.52	86.70
Dose3	2.46	0.31	19.23	-	-	-	-	-	-	0.00	0.00	
Circulatory Disease												
All	1.08	0.89	1.32	1.09	0.86	1.39	1.16	0.94	1.43	0.98	0.68	1.42
Dose1	0.99	0.73	1.34	0.91	0.64	1.29	1.18	0.81	1.73	0.90	0.56	1.44
Dose2	1.08	0.84	1.40	0.92	0.65	1.32	1.15	0.92	1.44	1.07	0.67	1.70
Dose3	1.13	0.89	1.45	**1.82**	**1.27**	**2.60**				1.08	0.34	3.44
Diabetes												
All	3.95	0.84	18.44	0.91	0.08	10.61	4.88	0.90	26.45	4.71	0.50	44.44
Dose1	**7.68**	**1.49**	**39.61**	-	-	-	4.51	0.40	51.31	-	-	-
Dose2	4.06	0.74	22.42	-	-	-	4.98	0.87	28.36	-	-	-
Dose3	0.93	0.08	10.52	-	-	-				-	-	-
Emphysema												
All	0.60	0.19	1.88	0.44	0.09	2.19	0.43	0.10	1.75	-	-	-
Dose1	1.06	0.21	5.28	-	-	-	-	-	-	-	-	-
Dose2	0.28	0.03	2.33	-	-	-	-	-	-	-	-	-
Dose3	0.65	0.16	2.65	-	-	-				-	-	-
IHD												
All	1.07	0.84	1.36	0.98	0.73	1.32	1.17	0.90	1.51	1.01	0.65	1.56
Dose1	1.13	0.80	1.60	0.84	0.54	1.29	1.46	0.96	2.24	1.05	0.62	1.79
Dose2	1.01	0.74	1.39	0.92	0.60	1.41	1.11	0.84	1.45	0.91	0.51	1.63
Dose3	1.07	0.79	1.46	1.40	0.86	2.27				1.49	0.46	4.81
Respiratory Disease												
All	1.23	0.79	1.90	1.33	0.80	2.21	1.23	0.78	1.94	1.06	0.49	2.32
Dose1	0.81	0.37	1.76	1.60	0.84	3.05	0.36	0.09	1.48	0.99	0.35	2.82
Dose2	1.08	0.61	1.92	1.25	0.63	2.50	1.40	0.88	2.21	0.94	0.36	2.43
Dose3	1.56	0.95	2.55	1.04	0.43	2.54				2.86	0.64	12.76

Note: For all deaths, circulatory disease, and ischaemic heart disease (IHD) the Poisson regression model included log age and whether the year of death occurred before or after 1960. For all other outcomes model included log age. Likelihood ratio confidence limits, 10 year exposure lag.
Significant results highlighted. – denotes failure to converge.
Dose indicates duration of exposure. For all except the DDT period of chemical use, "All" equates to any employment during this period, "Dose1" equates to less than 5 years employment, "Dose2" equates to 5 or more but less than 15 years of employment and "Dose3" equates to more than 15 years employment. For the DDT period, "Dose1" represents less than 3 years and "Dose2" represents 3 or more years of employment.

Table 4-26 Comparison between cancer deaths in Dippers and Controls by exposure group.

	All Chemical Periods (1935-95)			Arsenic Period (1935-55)			DDT Period (1955-62)			Modern Chemicals Period (1963-95)		
Dose	SIR	LCI	UCI	SIR	LCI	UCI	SIR	LCI	UCI	SIR	LCI	UCI
All Cancers												
All	1.24	0.93	1.66	1.11	0.78	1.58	1.21	0.89	1.64	1.29	0.80	2.07
Dose1	1.03	0.66	1.61	1.21	0.76	1.91	1.07	0.60	1.92	1.13	0.62	2.06
Dose2	1.16	0.80	1.69	0.95	0.57	1.60	1.24	0.90	1.70	1.30	0.70	2.41
Dose3	**1.49**	**1.05**	**2.13**	1.21	0.65	2.26				**2.94**	**1.03**	**8.34**
Bladder Cancer												
All	0.45	0.10	2.03	-	-	-	0.54	0.13	2.23	-	-	-
Dose1	-	-	-	-	-	-	-	-	-	-	-	-
Dose2	-	-	-	-	-	-	-	-	-	-	-	-
Dose3	-	-	-	-	-	-				-	-	-
Brain Cancer												
All	2.01	0.16	24.57	-	-	-	2.06	0.10	41.44	0.84	0.07	10.21
Dose1	-	-	-	-	-	-				-	-	-
Dose2	-	-	-	-	-	-	2.62	0.12	55.30	-	-	-
Dose3	-	-	-	-	-	-				-	-	-
Colon Cancer												
All	0.62	0.21	1.89	0.71	0.18	2.80	0.51	0.13	2.06	1.07	0.23	5.07
Dose1	-	-	-	-	-	-	-	-	-	-	-	-
Dose2	-	-	-	-	-	-	-	-	-	-	-	-
Dose3	-	-	-	-	-	-				-	-	-
Hodgkin's Disease												
All	-	-	-	-	-	-	-	-	-	-	-	-
Dose1	-	-	-	-	-	-	-	-	-	-	-	-
Dose2	-	-	-	-	-	-	-	-	-	-	-	-
Dose3	-	-	-	-	-	-				-	-	-
Lung Cancer												
All	1.33	0.80	2.21	1.14	0.61	2.12	1.21	0.71	2.07	1.10	0.50	2.43
Dose1	0.90	0.39	2.09	1.12	0.48	2.61	0.25	0.03	1.87	0.96	0.35	2.67
Dose2	1.55	0.83	2.87	1.46	0.67	3.16	1.41	0.82	2.43	1.19	0.44	3.21
Dose3	1.43	0.76	2.70	0.57	0.13	2.49				1.71	0.22	13.22
Lymphocytic Leukaemia												
All	1.42	0.18	11.54	-	-	-	0.90	0.07	11.45	7.45	0.33	170.74
Dose1	1.86	0.16	21.11	-	-	-	-	-	-	9.74	0.46	205.45
Dose2	1.79	0.14	22.14	-	-	-	-	-	-	0.00	0.00	-
Dose3	-	-	-	-	-	-				0.00	0.00	-

Note: Poisson regression adjusted for log age. Likelihood ratio confidence limits, 10 year exposure lag. Significant results highlighted. – denotes failure to converge.
Dose indicates duration of exposure. For all except the DDT period of chemical use, "All" equates to any employment during this period, "Dose1" equates to less than 5 years employment, "Dose2" equates to 5 or more but less than 15 years of employment and "Dose3" equates to more than 15 years employment. For the DDT period, "Dose1" represents less than 3 years and "Dose2" represents 3 or more years of employment.

Table 4-27 Comparison between cancer deaths in Dippers and Controls by exposure group

	All Chemical Periods (1935-95)			Arsenic Period (1935-55)			DDT Period (1955-62)			Modern Chemicals Period (1963-95)		
Dose	SIR	LCI	UCI	SIR	LCI	UCI	SIR	LCI	UCI	SIR	LCI	UCI
Melanoma												
All	1.06	0.09	11.98	-	-	-	-	-	-	2.86	0.21	39.67
Dose1	2.57	0.22	29.75	-	-	-	-	-	-	3.95	0.30	51.24
Dose2	0.00	0.00	-	-	-	-	-	-	-	-	-	-
Dose3	0.00	0.00	-	-	-	-				-	-	-
Multiple Myeloma												
All	0.65	0.04	10.62	-	-	-	-	-	-	-	-	-
Dose1	-	-	-	-	-	-	-	-	-	-	-	-
Dose2	-	-	-	-	-	-	-	-	-	-	-	-
Dose3	-	-	-	-	-	-				-	-	-
Myeloid Leukaemia												
All	1.15	0.25	5.39	0.60	0.06	6.05	1.64	0.30	8.98	1.94	0.25	15.39
Dose1	1.15	0.12	11.21	1.62	0.16	15.83	2.99	0.30	29.76	1.83	0.16	21.13
Dose2	0.00	0.00	-	0.00	0.00	-	1.32	0.20	8.69	-	-	-
Dose3	3.92	0.65	23.63	0.00	0.00	-				**20.90**	**1.54**	**284.41**
NHL												
All	3.98	0.45	35.30	5.33	0.52	54.19	5.56	0.57	54.08	-	-	-
Dose1	-	-	-	-	-	-	-	-	-	-	-	-
Dose2	-	-	-	-	-	-	-	-	-	-	-	-
Dose3	-	-	-	-	-	-	-	-	-	-	-	-
Other Skin												
All	-	-	-	-	-	-	-	-	-	-	-	-
Dose1	-	-	-	-	-	-	-	-	-	-	-	-
Dose2	-	-	-	-	-	-	-	-	-	-	-	-
Dose3	-	-	-	-	-	-	-	-	-	-	-	-
Pancreatic Cancer												
All	2.89	0.60	13.85	3.13	0.56	17.62	2.72	0.67	11.01	-	-	-
Dose1	1.54	0.14	17.01	-	-	-	**7.00**	**1.39**	**35.32**	-	-	-
Dose2	2.07	0.29	14.93	-	-	-	1.82	0.39	8.49	-	-	-
Dose3	4.79	0.86	26.59	-	-	-				-	-	-
Prostate Cancer												
All	1.20	0.50	2.85	1.39	0.52	3.73	0.97	0.38	2.51	0.99	0.24	4.07
Dose1	1.95	0.64	5.97	0.96	0.20	4.50	1.39	0.30	6.47	-	-	-
Dose2	0.67	0.18	2.53	0.92	0.19	4.35	0.89	0.32	2.46	-	-	-
Dose3	1.26	0.45	3.55	2.94	0.83	10.41				-	-	-
Rectal Cancer												
All	2.51	0.49	12.93	3.46	0.61	19.73	4.01	0.71	22.72	1.03	0.06	17.49
Dose1	1.58	0.14	17.44	4.06	0.57	29.08	-	-	-	-	-	-
Dose2	2.36	0.32	17.31	2.24	0.20	25.65	-	-	-	-	-	-
Dose3	3.69	0.54	25.05	4.72	0.37	60.61	-	-	-	-	-	-
Stomach Cancer												
All	3.32	0.70	15.67	3.40	0.60	19.31	3.08	0.75	12.61	2.79	0.23	33.85
Dose1	3.08	0.43	21.85	2.03	0.18	22.61	5.13	0.84	31.36	2.89	0.17	47.78
Dose2	4.05	0.73	22.40	4.50	0.61	33.46	2.62	0.59	11.62	2.99	0.16	55.91
Dose3	2.76	0.44	17.33	4.76	0.37	61.41				-	-	-

Note: Poisson regression adjusted for log age. Likelihood ratio confidence limits, 10 year exposure lag. Significant results highlighted. – denotes failure to converge.
Dose indicates duration of exposure. For all except the DDT period of chemical use, "All" equates to any employment during this period, "Dose1" equates to less than 5 years employment, "Dose2" equates to 5 or more but less than 15 years of employment and "Dose3" equates to more than 15 years employment. For the DDT period, "Dose1" represents less than 3 years and "Dose2" represents 3 or more years of employment.

4.4 SPECIFIC OUTCOMES

4.4.1 All Cause Mortality

As described above, when all cause mortality was compared with the Australian population, Dippers as a whole had death rates significantly above the general community (SMR 1.10; 95% CI 1.01-1.19). Under the general model used in this study, there were 607 deaths among all Dippers when 552.8 might have been expected, an excess of 54.2 deaths over the study period.

Mortality was also increased when compared to the control group, although this was not statistically significant (SIR 1.09; 95% CI 0.96-1.25). As duration of employment as a Dipper increased, so mortality increased, both when compared with the Australian community and with the control population. In both analyses, mortality in the group of Dippers working more than 15 years was significantly greater than expected (SMR 1.19; 95% CI 1.04-1.35. SIR 1.25; 95% CI 1.05-1.49).

When compared with the Australian population, there was a similar statistically significant increase in all cause mortality for controls (SMR 1.15; 95% CI 1.03-1.28), while mortality for Dippers not yet working ten years was as expected (SMR 1.01, 95% CI 0.81-1.25).

As described in the Methods section, one of the assumptions of the study's general model was for a minimum 10 year lag interval between commencement of employment (and entry into the study) and date of death. A number of variations to this model were explored for all cause SMRs. The influence of changing the lag period on all cause mortality can be seen in Table 4-28. As the lag period was increased to 20 years, the SMR for tick dippers increased marginally from 1.09 to 1.12, remaining statistically significant for all models.

Table 4-28 Effect of different lag models on deaths from all causes versus Australian deaths (1935-1995) SMR adjusted for age at death & period of follow-up.

GROUP	OBS	EXP	SMR	LCI	UCI
No Lag Period	692	635.95	1.09	1.01	1.17
5 Year Lag Period	665	602.17	1.10	1.02	1.19
10 Year Lag Period	607	552.84	1.10	1.01	1.19
15 Year Lag Period	548	489.57	1.12	1.03	1.22
20 Year Lag Period	460	409.09	1.12	1.02	1.23

4.4.2 Cancer Mortality

There was an increase in cancer mortality of borderline statistical significance for Dippers as a group when compared to the Australian population (SMR 1.16; 95% CI 0.98-1.37). This equated to 21 more deaths in the exposed cohort than would have been expected over the total study period. Of these, 12 were due to lung cancer. When Dippers as a group were compared with controls, there was also a small increase in cancer mortality but this was not statistically significant (SIR 1.12; 95% CI 0.86-1.46). Mortality from cancer was significantly increased compared to controls for Dippers working over 15 years (SIR 1.49; 95% CI 1.05-2.13), and there was also an increase of borderline statistical significance when this group was compared to the Australian population (SMR 1.30; 95% CI 0.99-1.68). There was a gradient of increasing mortality with increasing duration of employment, although both controls (SMR 1.07; 95% CI 0.83-1.35) and Dippers not yet over the 10 year exposure lag (SMR 1.24; 95% CI 0.71-2.01) also tended to have higher than expected mortality.

SMRs were also calculated for deaths from total cancers using variations in lag period (Table 4-29).

Table 4-29 Effect Of Different Lag Models On Deaths Among All Dippers From All Cancers Versus Aus Deaths (1945-1995)

GROUP	OBS	EXP	SMR	LCI	UCI
No Lag Period	168	141.96	**1.18**	**1.01**	**1.38**
5 Year Lag Period	164	136.42	**1.20**	**1.03**	**1.40**
10 Year Lag Period	148	127.06	1.16	0.98	1.37
15 Year Lag Period	133	113.65	1.17	0.98	1.39
20 Year Lag Period	117	95.22	**1.23**	**1.02**	**1.47**

While the SMR for exposed subjects remained similar for all lag models, applying a 10 or 15-year lag to the model resulted in this not reaching statistical significance.

A range of models in addition to the default were also applied to analysis of specific cancers. These identified a significant increase in mortality in only one cancer not already identified by the default analysis. When mortality from Non Hodgkin's Lymphoma (NHL) among Dippers working during the period of modern chemical use was extended to include subjects who had also worked in other chemical periods, the SMR and lower confidence limit both increased (Table 4-30). When NHL mortality among this same exposure group was compared to controls (Table 4-31), the increase in Standardized Incidence Ratio for all exposed subjects was of borderline significance (SIR 8.71; 95% CI 0.97-78.12) and this was statistically significant for Dippers working between 5 and 15 years (SIR 11.60; 95% CI 1.11-121.74).

Table 4-30 SMRs for NHL for subjects working in the modern chemical era but commencing at any time in the study

DOSE	OBS	EXP	SMR	LCI	UCI
Controls	1	2.02	0.50	0.01	2.76
All	5	2.25	2.22	0.72	5.18
Dose0	0	1.36	0.00	0.00	2.20
Dose1	1	0.80	1.25	0.03	6.98
Dose2	3	1.12	2.69	0.55	7.86
Dose3	1	0.34	2.93	0.07	16.34

Note: Person years analysis adjusted for age, period of follow-up

Table 4-31 SIRs for NHL for subjects working in the modern chemical era but commencing at any time in the study

	SIR	LCL	UCL
All	8.71	0.97	78.12
DOSE1	4.52	0.28	73.42
DOSE2	**11.60**	**1.11**	**121.74**
DOSE3	14.26	0.81	251.30

Note: Poisson regression adjusted for age. Likelihood ratio confidence limits

4.4.3 Pancreatic Cancer

As described above, death rates from pancreatic cancer were found to be raised for Dippers working for less than 3 years during the DDT period, both compared with the Australian population (SMR 5.27; 95% CI 1.09-15.40), and in the internal comparison between Dippers and Controls (SIR 7.00; 95% CI 1.39-35.32).

There were 12 deaths from pancreatic cancer in study subjects, 10 in Dippers and 2 in controls. All but one Dipper death occurred more than 10 years after commencing employment. Two subjects, both Dippers, had incomplete data on duration of employment. Of the remaining 8 Dippers, all worked during the DDT era, 4 worked during the arsenic era and 8 worked during the era of modern chemical use. There were no deaths from pancreatic cancer among Dippers working exclusively during either the modern or arsenic eras.

The DDT era was defined in the general model as the period between 1955, when DDT came into use, until 1962 when it was rapidly phased out. However, it was only during the last few years of this period that DDT became the dominant chemical in use in dips. It is therefore likely that many subjects working during the early years of this era were only occasionally exposed to DDT, or even not at all. The chances of a Dipper being exposed to DDT should therefore be higher for the later years of this period, and analysis of these years may give a more accurate impression of any mortality that might be attributable to this chemical. SIR and SMR analysis was therefore undertaken for Dippers as a group, using a range of year criteria to define the DDT exposed era (Table 4-32, Table 4-33). In general, there is a tendency for both the SIR and SMR to increase and for the statistical significance to increase with a tighter focus on the later years of DDT use. However, both the maximum SMR (SMR 2.41; 95% CI 0.89-5.25) and the maximum SIR (SIR 4.73; 95% CI 0.89-25.15) remain short of statistical significance.

In an attempt to increase analytical power, comparison was also made between exposed Dippers and controls comprising both the standard control group of Council workers and Dippers who either never worked during the DDT era or had not yet passed the 10 year exposure lag. This comparison also demonstrated a trend for the SIR to increase with a tighter

focus on the later years of DDT use (Table 4-34). Many of these increases were also statistically significant.

Table 4-32 Standardised Incidence Ratios (SIR) for pancreatic cancer using different year criteria to define DDT period

Period definition	P value	SIR	LCL	UCL
1955-62	0.16	2.72	0.67	11.01
1956-62	0.15	2.82	0.69	11.45
1957-62	0.13	2.92	0.72	11.89
1958-62	0.12	3.04	0.74	12.41
1959-62	0.11	3.14	0.76	12.89
1960-62	0.17	2.73	0.64	11.56
1961-62	0.08	4.41	0.84	23.23
1962	0.07	4.73	0.89	25.15

Note: Poisson regression adjusted for age. Likelihood ratio confidence limits

Table 4-33 Standardised Mortality Ratios (SMR) for pancreatic cancer using different year criteria to define DDT period

Period definition	Observed	Expected	SMR	LCL	UCL
1955-1962	7	3.54	1.98	0.79	4.07
1956-1962	7	3.47	2.02	0.81	4.15
1956-1962	7	3.41	2.05	0.83	4.23
1958-1962	7	3.34	2.10	0.84	4.32
1959-1962	7	3.25	2.15	0.87	4.43
1960-1962	6	2.89	2.08	0.76	4.52
1961-1962	6	2.68	2.24	0.82	4.88
1962	6	2.49	2.41	0.89	5.25

Note: Person years analysis adjusted for age, period of follow-up

Table 4-34 Standardised Incidence Ratios (SIR) for pancreatic cancer using different year criteria to define DDT period including non-exposed dippers in control group

Period definition	P value	SIR	LCL	UCL
1955-62	0.06	3.76	0.93	15.24
1956-62	0.06	3.89	0.96	15.78
1957-62	0.05	4.00	0.98	16.26
1958-62	**0.05**	**4.14**	**1.01**	**16.87**
1959-62	**0.04**	**4.26**	**1.04**	**17.46**
1960-62	0.07	3.72	0.88	15.75
1961-62	**0.03**	**5.99**	**1.14**	**31.55**
1962	**0.03**	**6.44**	**1.22**	**34.13**

Note: Poisson regression adjusted for age. Likelihood ratio confidence limits

The impact of using differing lag periods within the model was also explored (Table 4-35). Lags of 5, 10, 15 or 20 years made little difference to SMRs, although the general model used (lag 10 years) produced the estimate with the lowest SMR and lower confidence limit.

Table 4-35 Effect of different lag periods on pancreatic cancer SMR during the era of DDT use (1955-62)

Lag Period	Observed	Expected	SMR	LCL	UCL
5 Years	8	3.83	2.09	0.90	4.11
10 Years	7	3.54	1.98	0.79	4.07
15 Years	7	3.12	2.25	0.90	4.63
20 Years	6	2.54	2.36	0.87	5.14

Note: Person years analysis adjusted for age, period of follow-up

4.4.4 Asthma

Asthma was identified as a cause of death in 16 subjects: 5 controls and 11 Dippers. For 9 of these, 2 controls and 7 Dippers, asthma was identified as the underlying cause of death.

Mortality from asthma was significantly raised in all Dippers when compared to the Australian population (SMR 2.92; 95% CI 1.17-6.01). This was greatest among Dippers working in the era of modern chemicals (SMR 5.62; 95% CI 1.16-16.43). When the modern chemical period was limited to exposure before 1976, mortality was also significantly increased (SMR 5.82; 95% CI 1.20-17.00). Mortality was also significantly raised among Dippers working between 5 and15 years in the total modern chemical period (SMR 9.31; 95% CI 1.13-33.62).

There was also a smaller increase in mortality among controls, both for the total study period, and during the era of modern chemical use, although none of these increases were statistically significant. There were no deaths among Dippers not yet past the 10 year exposure lag.

When mortality was compared between Dippers and the control subcohort, deaths from asthma were more frequent in Dippers as a group, but this was not statistically significant (SIR 3.09 95% CI 0.62-15.52). There were also non-significant increases in SIR across all periods, greatest in the modern era (SIR 4.38; 95% CI 0.42-45.78).

Controls also showed increased mortality during this period, but the increase was neither as large as among Dippers, nor was it statistically significant. There was also a gradient of increasing SMRs across increasing duration of employment for subjects in the modern era, apart from the maximum exposure group. However, only 0.02 deaths were expected for this latter group and even one death would suggest mortality far in excess of that identified in other cells. For more meaningful comparison, further analysis was undertaken reducing the number of exposure categories from 3 to 2 (<10years, >=10 years). In this analysis, mortality in the highest exposure group was significantly increased both for subjects with known and estimated durations of employment (Table 4-36).

Table 4-36 SIRs for asthma during the modern chemical period using two duration of employment categories

DOSE	PVAL	SIR	LCL	UCL
Known durations of employment				
<10YRS	0.64	1.96	0.11	33.63
>=10YRS	0.04	**15.25**	**1.16**	**200.77**
Including estimated durations of employment				
<10YRS	0.64	1.95	0.12	33.10
>=10YRS	0.05	**12.84**	**1.03**	**160.71**

Note: Poisson regression adjusted for age. Likelihood ratio confidence limits

When the general model compared mortality for Dippers against both the Australian population and controls in the modern chemical period, subjects starting before the start of the period (1963) were excluded. SIR and SMR analyses were also run including subjects employed before 1963, but who still worked in the modern era (Table 4-37 Table 4-38). Mortality remained raised for this larger group, and these results became more statistically significant in the comparison between Dippers and controls.

Table 4-37 SIRs for asthma for subjects working in the modern chemical era but commencing at any time in the study

	P Value	SIR	LCL	UCL
All	0.24	2.16	0.55	8.51
Dose1	0.91	1.10	0.12	9.93
Dose2	0.07	3.76	0.86	16.33
Dose3	0.00	1.00	0.00	0.00

Note: Poisson regression adjusted for age. Likelihood ratio confidence limits

Table 4-38 SMRs for asthma for subjects working in the modern chemical era but commencing at any time in the study

DOSE	OBS	EXP	SMR	LCI	UCI
Controls	2	0.97	2.07	0.25	7.48
All	5	1.26	**3.96**	**1.29**	**9.25**
Dose0	2	1.10	1.83	0.22	6.59
Dose1	1	0.46	2.19	0.06	12.20
Dose2	4	0.64	**6.26**	**1.71**	**16.04**
Dose3	0	0.17	0.00	0.00	18.00

Note: Person years analysis adjusted for age, period of follow-up

The identified increase in mortality persisted regardless of the lag period used, however for some of these periods it lost statistical significance (Table 4-39).

Table 4-39 SMRs for asthma in all Dippers under differing lag criteria

Lag Period	SMR	LCL	UCL
No lag	3.88	0.80	11.33
5 years	4.54	0.94	13.28
10 years	**5.62**	**1.16**	**16.43**
15 years	5.17	0.63	18.67
20 years	**9.29**	**1.13**	**33.57**

Note: Person years analysis adjusted for age, period of follow-up

Asthma related issues were also reported more commonly by Dippers responding to the study survey after adjusting for age and smoking. Not only did responding Dippers report more asthma (OR 1.61, 95% CI 1.06-2.46), but they also reported more asthma in their offspring (OR 1.47, 95% CI 1.02-2.12), as well as more dermatitis/eczema, an atopic complaint linked to asthma (OR 1.61; 95% CI 1.02-2.55). These associations were spread fairly widely across different types of occupational pesticide exposure reported by subjects (Table 4-40).

Table 4-40 Odds ratios for asthma in subjects with different self reported occupational pesticide exposures after adjusting for age and smoking

	Odds Ratio	Lower Confidence Limit	Upper Confidence Limit	P Value
Dipper	**1.59**	**1.05**	**2.43**	0.03
Arsenic	**2.46**	**1.49**	**4.08**	0.00
Organochlorines	**1.81**	**1.16**	**2.84**	0.01
Organophosphates	**1.55**	**1.01**	**2.38**	0.04
Carbamates	1.50	0.98	2.30	0.06
Pyrethrins	**1.55**	**1.01**	**2.38**	0.05
Herbicides	1.32	0.86	2.02	0.20
Fungicides	**2.44**	**1.40**	**4.25**	0.00
All Modern Pesticides	1.53	0.96	2.43	0.08

Note: Logistic regression by group (Dipper or control) adjusted for log age, ever smoked

4.4.5 Diabetes

16 subjects were identified as having diabetes as an underlying cause of death: 2 controls and 14 dippers. A further Dipper with an underlying cause of death of lung cancer had diabetes listed as one of the four causes of death on their death certificate. Of the Dippers with full employment details, none worked exclusively in the arsenic period, 7 worked during the DDT period and 6 worked in the modern chemical period.

When compared to the total Australian population, Dippers as a group had increased mortality from diabetes (SMR 1.51; 95% CI 0.78-2.64), increasing towards the end of the study period to a maximum for workers in the modern chemical era (SMR 3.00, 95% CI 0.97-7.00). This increase was statistically significant for Dippers working during the first half of this period (SMR 3.08; 95% CI 1.00-7.20), and for those working less than five years over the total study period (SMR 3.57; 95% CI 1.16-8.32). When compared with the Australian population, mortality from diabetes tended to be slightly reduced for controls, and slightly elevated for Dippers who had not yet worked 10 years. These trends were not statistically significant.

Varying the lag period made little difference to SMRs, although for the modern chemical era they were generally statistically significant under other lag models apart from a 20 year lag where the confidence interval broadened considerably (Table 4-41).

Table 4-41 Standardised Mortality Ratios diabetes during the total modern chemical era, varying lags

Lag Period	Observed	Expected	SMR	LCL	UCL
Known duration of employment					
No lag	6	2.15	**2.80**	**1.03**	**6.09**
5 years	6	1.97	**3.05**	**1.12**	**6.64**
10 years	5	1.67	3.00	0.97	6.99
15 years	5	1.28	**3.91**	**1.27**	**9.13**
20 years	3	0.79	3.79	0.78	11.07

Note: Person years analysis adjusted for age, period of follow-up

For all periods apart from the arsenic era, mortality from diabetes was also increased for Dippers as a group when compared to controls, although none of these increases were statistically significant (Table 4-42). There was, however, a statistically significant increase in

mortality for Dippers working less than 5years over the total study period (SIR 7.68; 95% CI 1.49-39.61). Risk by duration of exposure could not be calculated for either the arsenic or modern chemical period due to small numbers. However, when the modern chemical period was limited to the period 1963-76, the SIR was greater than for the whole period (1963-96), although this was not of statistical significance (SIR 5.78; 95% CI 0.65-51.72).

When Dippers not yet past the 10 year exposure lag or exposed during other periods were included in the control group, the pattern of SIRs was similar, although reduced for both the DDT and modern period.

Table 4-42 Comparison of mortality from diabetes in Dippers compared to different control groups

	All Chemical Periods (1935-95)			Arsenic Period (1935-55)			DDT Period (1955-62)			Modern Chemicals Period (1963-95)		
Dose	SIR	LCI	UCI	SIR	LCI	UCI	SIR	LCI	UCI	SIR	LCI	UCI
Controls including unexposed dippers												
All	3.10	0.82	11.69	0.26	0.03	2.00	1.43	0.46	4.43	2.62	0.45	15.28
Dose1	**6.08**	**1.45**	**25.51**	-	-	-	1.44	0.18	11.82	-	-	-
Dose2	3.17	0.69	14.45	-	-	-	1.43	0.43	4.69	-	-	-
Dose3	0.71	0.07	7.11	-	-	-	-	-	-	-	-	-
Controls limited to council workers												
All	3.95	0.84	18.44	0.91	0.08	10.61	4.88	0.90	26.45	4.71	0.50	44.44
Dose1	**7.68**	**1.49**	**39.61**	-	-	-	4.51	0.40	51.31	-	-	-
Dose2	4.06	0.74	22.42	-	-	-	4.98	0.87	28.36	-	-	-
Dose3	0.93	0.08	10.52	-	-	-				-	-	-

There was no tendency for mortality from diabetes to increase in the later DDT period (Table 4-43).

Table 4-43 Mortality from diabetes compared to controls for late DDT Period (1960-62)

Dose	SIR	LCI	UCI
All	1.42	0.29	6.99
Dose1	3.63	0.62	21.34
Dose2	0.63	0.07	6.05

To help convergence of the analysis for the modern chemical period, exposure categories were reduced from 3 to 2 (<10 years, >=10years). When this model was applied there was a trend for increasing mortality with increased exposure but neither dose level was significant (Table 4-44).

Table 4-44 Standardised Incidence ratios for diabetes in the modern chemical period using two duration of employment categories

DOSE	PVAL	SIR	LCL	UCL
Known durations of employment				
<10YRS	0.20	4.54	0.45	45.70
>=10YRS	0.25	5.36	0.31	91.32

Note: Poisson regression adjusted for age. Likelihood ratio confidence limits

There was also a slightly increased self reported prevalence of diabetes in dippers compared to controls among surviving cohort members, although this was not significant (OR 1.14; 95% CI 0.60-2.19). 44 subjects reported suffering from diabetes, 23 controls and 21 Dippers. When the odds ratios were calculated for different occupational pesticide exposures reported in this survey, most hovered around unity (Table 4-45). One notable exception was occupational exposure to herbicides for which there were significantly raised odds (OR 2.26; 95% CI 1.15-4.43). This relationship remained significant after adjusting for cohort group (Table 4-46). The strength of this relationship was also distinctive from other outcomes assessed by reported herbicide exposure (Table 4-10).

Table 4-45 Odds ratios for diabetes in subjects with different self reported occupational pesticide exposure

	Odds Ratio	Lower Confidence Limit	Upper Confidence Limit	P Value
Dipper	1.13	0.59	2.16	0.71
Arsenic	1.23	0.61	2.48	0.57
Organochlorines	1.10	0.56	2.12	0.79
Organophosphates	1.16	0.61	2.21	0.66
Carbamates	0.87	0.44	1.71	0.68
Pyrethrins	1.28	0.66	2.52	0.47
Herbicides	**2.27**	**1.16**	**4.44**	**0.02**
Fungicides	0.63	0.19	2.12	0.46
Modern Pesticides	1.94	0.93	4.05	0.08

Note: Logistic regression by group (Dipper or control) adjusted for log age, ever smoked

Table 4-46 Results of Logistic Regression for Diabetes and self reported herbicide exposure by log age, ever smoked and cohort group

	Odds Ratio	Lower Confidence Limit	Upper Confidence Limit	P Value
INTERCEPT	0.00	0.00	0.00	0.00
LNAGE	14.43	3.66	56.88	0.00
SMOKE	1.97	0.88	4.38	0.10
GROUPC	0.93	0.48	1.77	0.81
GROUPT	1.00	1.00	1.00	.
HERB	2.24	1.14	4.38	0.02
SCALE	2.72	2.72	2.72	.

Note: Logistic regression by group (Dipper or control) adjusted for log age, ever smoked

4.4.6 Deaths from Diseases of the Central Nervous System

As outlined above, the survey of surviving subjects included a neuropsychological screening questionnaire, and the total scores of Dippers on this screening instrument were significantly worse than those of control subjects. A range of central nervous system (CNS) disorders, including Parkinson's disease have also been identified by other studies as possibly associated with pesticide exposure. The study database was therefore explored for any other evidence of CNS diseases. Very few subjects died of Central Nervous System diseases during the study period. Two Dippers and two control subjects had Parkinson's disease identified as the underlying cause of death. One further Dipper had Parkinson's disease recorded as one of the four possible notified causes of death. All subjects worked during the early years of the study and the youngest age at death amongst the group was 70 years.

A comparison was also undertaken of deaths in Dippers and controls due to all diseases of the central nervous system (ICD 319.9-350). Central nervous system mortality identified as an underlying cause of death in Dippers was reduced (SIR 0.49; 95% CI 0.11-2.23), although numbers were small and assessment by exposure group was not possible. When the analysis was expanded to include any recorded cause of death, there was also no significant difference between the groups (Table 4-47). Numbers in the modern chemical period, during which most chemicals considered likely to act on the central nervous system were in use, were too small to for statistical analysis.

Table 4-47 Deaths from Diseases of the Central Nervous System recorded as any cause of death

Exposure Group	P Value	SIR	LCL	UCL
All	0.81	1.16	0.34	4.03
1	0.61	1.55	0.28	8.46
2	0.93	0.93	0.17	5.09
3	0.85	1.16	0.25	5.34

Deaths from mental disorders were also rare. When the two subcohorts were compared for mental disorders as an underlying cause of death there was a non-significant increase in mortality between Dippers and controls, and numbers were too small for assessment by exposure group (SIR 1.70; 95% CI 0.30-9.73).

4.4.7 Lung cancer, ischaemic heart disease, circulatory disease, respiratory disease and emphysema

Between them, these traditionally smoking related diseases were responsible for 436 deaths among Dippers after the model lag period of 10 years had passed. SMRs for Dippers as a group were increased for all these diseases, and many of these increases were statistically significant (Table 4-48). Mortality from all of these diseases was also increased in the control group of Council workers and, in several instances, among the group of Dippers who had not yet worked 10 years.

There are few obvious trends in the mortality patterns of these diseases across the study period. For most diseases over most periods, SMRs for controls actually exceed Dippers as a group. This is reflected in SIR's close to unity for all diseases except pancreatic cancer (Table 4-49). Mortality is also high for Dippers who had not yet worked 10 years in a particular study period. Few diseases show the trend of increasing mortality with increasing duration of exposure that might be expected if employment was the direct cause of the disease.

Changing the lag period had little effect on mortality estimates or confidence intervals (Table 4-50).

Table 4-48 Standardised Mortality Ratios for Dippers and Controls

Exposure Group	All Chemical Periods (1935-95)			Arsenic Period (1935-55)			DDT Period (1955-62)			Modern Chemical Period (1963-95)		
	SMR	LCI	UCI	SMR	LCI	UCI	SMR	LCI	UCI	SMR	LCI	UCI
Circulatory Disease												
Controls	1.11	0.94	1.31	1.07	0.80	1.41	1.11	0.90	1.36	1.19	0.87	1.59
All	1.08	0.95	1.23	0.93	0.75	1.15	1.09	0.94	1.25	1.13	0.83	1.49
Dose 0	1.00	0.68	1.42							1.17	0.75	1.72
Dose 1	1.11	0.83	1.45	0.72	0.44	1.11	1.10	0.75	1.56	1.11	0.71	1.67
Dose 2	1.03	0.83	1.27	0.83	0.56	1.18	1.06	0.92	1.27	1.22	0.86	1.79
Dose 3	1.12	0.92	1.34	1.26	0.89	1.74				1.74	0.36	5.08
Emphysema												
Controls	2.69	0.99	5.85	2.89	0.35	10.45	2.67	0.73	6.83	2.78	0.34	10.06
All	1.53	0.56	3.32	0.77	0.02	4.28	1.02	0.21	2.99	3.41	0.70	9.97
Dose 0	0.00	0.00	10.55							0.00	0.00	13.00
Dose 1	2.63	0.32	9.49	2.66	0.07	14.81	0.00	0.00	7.06	5.16	0.63	18.65
Dose 2	0.70	0.02	3.91	0.00	0.00	5.89	1.20	0.25	3.50	2.23	0.06	12.42
Dose 3	1.72	0.35	5.02	0.00	0.00	7.21				0.00	0.00	69.27
Ischaemic Heart Disease												
Controls	**1.38**	**1.13**	**1.68**	**1.80**	**1.29**	**2.45**	**1.38**	**1.08**	**1.74**	1.31	0.91	1.83
All	**1.37**	**1.18**	**1.59**	**1.36**	**1.02**	**1.78**	**1.31**	**1.09**	**1.56**	1.28	0.91	1.76
Dose 0	**2.21**	**1.38**	**3.34**							1.53	0.91	2.42
Dose 1	**1.70**	**1.24**	**2.29**	0.85	0.44	1.48	**2.09**	**1.37**	**3.07**	1.32	0.79	2.06
Dose 2	1.25	0.95	1.62	1.56	0.98	2.37	1.20	0.98	1.45	1.14	0.65	1.85
Dose 3	**1.32**	**1.03**	**1.66**	**1.79**	**1.07**	**2.79**				2.55	0.53	7.46
Respiratory Disease												
Controls	**1.50**	**1.02**	**2.12**	1.29	0.59	2.44	1.43	0.87	2.21	1.92	0.99	3.36
All	**1.61**	**1.24**	**2.07**	**1.72**	**1.10**	**2.55**	**1.60**	**1.16**	**2.13**	**1.87**	**1.02**	**3.14**
Dose 0	0.52	0.06	1.87							0.00	0.00	1.17
Dose 1	1.09	0.47	2.14	**2.36**	**1.08**	**4.49**	0.45	0.06	1.64	1.52	0.49	3.54
Dose 2	1.39	0.84	2.17	1.67	0.76	3.17	**1.81**	**1.31**	**2.43**	1.83	0.73	3.76
Dose 3	**2.03**	**1.41**	**2.84**	1.25	0.46	2.73				5.68	0.69	20.52
Bladder Cancer												
Controls	2.27	0.62	5.82	1.84	0.05	10.23	3.41	0.93	8.74	0.00	0.00	5.37
All	0.96	0.20	2.80	0.00	0.00	2.78	1.30	0.27	3.79	0.00	0.00	4.45
Dose 0	7.67	0.93	27.70							0.00	0.00	15.94
Dose 1	0.00	0.00	4.86	0.00	0.00	10.04	0.00	0.00	8.32	0.00	0.00	10.24
Dose 2	0.89	0.02	4.94	0.00	0.00	7.11	1.54	0.32	4.49	0.00	0.00	8.64
Dose 3	1.44	0.17	5.19	0.00	0.00	8.39				0.00	0.00	86.91
Lung Cancer												
Controls	1.13	0.71	1.71	1.37	0.59	2.69	0.98	0.51	1.72	1.57	0.78	2.81
All	1.34	0.97	1.81	1.08	0.54	1.93	1.27	0.85	1.83	1.51	0.78	2.63
Dose 0	1.73	0.64	3.77							1.05	0.22	3.06
Dose 1	0.97	0.39	1.99	1.34	0.43	3.12	0.28	0.00	1.56	1.31	0.43	3.06
Dose 2	1.59	0.94	2.51	1.01	0.27	2.58	1.45	0.97	2.10	1.61	0.59	3.49
Dose 3	1.34	0.80	2.12	0.80	0.10	2.89				2.38	0.06	13.25

Note: Indirect standardisation to Australian population, person years analysis, confidence intervals determined by Poisson regression. 10 year exposure lag.
Significant results highlighted.
Dose indicates duration of exposure. Dose 0 relates to period of follow-up of exposed subjects before 10 year exposure lag passed. For all except the DDT period of chemical use, "All" equates to any employment during this period, "Dose1" equates to less than 5 years employment, "Dose2" equates to 5 or more but less than 15 years of employment and "Dose3" equates to more than 15 years employment. For the DDT period, "Dose1" represents less than 3 years and "Dose2" represents more than 3 years of employment

Table 4-49Comparison of Mortality in Dippers and Controls for smoking related disease

	All Chemical Periods (1935-95)			Arsenic Period (1935-55)			DDT Period (1955-62)			Modern Chemicals Period (1963-95)		
Dose	SIR	LCI	UCI	SIR	LCI	UCI	SIR	LCI	UCI	SIR	LCI	UCI
Circulatory Disease												
All	1.08	0.89	1.32	1.09	0.86	1.39	1.16	0.94	1.43	0.98	0.68	1.42
Dose1	0.99	0.73	1.34	0.91	0.64	1.29	1.18	0.81	1.73	0.90	0.56	1.44
Dose2	1.08	0.84	1.40	0.92	0.65	1.32	1.15	0.92	1.44	1.07	0.67	1.70
Dose3	1.13	0.89	1.45	**1.82**	**1.27**	**2.60**				1.08	0.34	3.44
Emphysema												
All	0.60	0.19	1.88	0.44	0.09	2.19	0.43	0.10	1.75	-	-	-
Dose1	1.06	0.21	5.28	-	-	-	-	-	-	-	-	-
Dose2	0.28	0.03	2.33	-	-	-	-	-	-	-	-	-
Dose3	0.65	0.16	2.65	-	-	-				-	-	-
IHD												
All	1.07	0.84	1.36	0.98	0.73	1.32	1.17	0.90	1.51	1.01	0.65	1.56
Dose1	1.13	0.80	1.60	0.84	0.54	1.29	1.46	0.96	2.24	1.05	0.62	1.79
Dose2	1.01	0.74	1.39	0.92	0.60	1.41	1.11	0.84	1.45	0.91	0.51	1.63
Dose3	1.07	0.79	1.46	1.40	0.86	2.27				1.49	0.46	4.81
Respiratory Disease												
All	1.23	0.79	1.90	1.33	0.80	2.21	1.23	0.78	1.94	1.06	0.49	2.32
Dose1	0.81	0.37	1.76	1.60	0.84	3.05	0.36	0.09	1.48	0.99	0.35	2.82
Dose2	1.08	0.61	1.92	1.25	0.63	2.50	1.40	0.88	2.21	0.94	0.36	2.43
Dose3	1.56	0.95	2.55	1.04	0.43	2.54				2.86	0.64	12.76
Bladder Cancer												
All	0.45	0.10	2.03	-	-	-	0.54	0.13	2.23	-	-	-
Dose1	-	-	-	-	-	-	-	-	-	-	-	-
Dose2	-	-	-	-	-	-	-	-	-	-	-	-
Dose3	-	-	-	-	-	-				-	-	-
Lung Cancer												
All	1.33	0.80	2.21	1.14	0.61	2.12	1.21	0.71	2.07	1.10	0.50	2.43
Dose1	0.90	0.39	2.09	1.12	0.48	2.61	0.25	0.03	1.87	0.96	0.35	2.67
Dose2	1.55	0.83	2.87	1.46	0.67	3.16	1.41	0.82	2.43	1.19	0.44	3.21
Dose3	1.43	0.76	2.70	0.57	0.13	2.49				1.71	0.22	13.22
Pancreatic Cancer												
All	2.89	0.60	13.85	3.13	0.56	17.62	2.72	0.67	11.01	-	-	-
Dose1	1.54	0.14	17.01	-	-	-	**7.00**	**1.39**	**35.32**	-	-	-
Dose2	2.07	0.29	14.93	-	-	-	1.82	0.39	8.49	-	-	-
Dose3	4.79	0.86	26.59	-	-	-				-	-	-

Note: Poisson regression adjusted for log age. Likelihood ratio confidence limits, 10 year exposure lag. Significant results highlighted. – denotes failure to converge.
Dose indicates duration of exposure. For all except the DDT period of chemical use, "All" equates to any employment during this period, "Dose1" equates to less than 5 years employment, "Dose2" equates to 5 or more but less than 15 years of employment and "Dose3" equates to more than 15 years employment. For the DDT period, "Dose1" represents less than 3 years and "Dose2" represents 3 or more years of employment.

Table 4-50 SMR smoking related diseases, differing lag periods

Lag Period	Ischaemic Heart Disease			Circulatory Disease			Respiratory Disease			Lung Cancer			Emphysema		
	SMR	LCL	UCL	SMR	LCL	UCL	SMR	LCL	UCL	SMR	LCL	UCL	SMR	LCL	UCL
0 yrs	**1.42**	**1.23**	**1.63**	1.07	0.95	1.21	**1.51**	**1.16**	**1.94**	**1.38**	**1.02**	**1.83**	1.42	0.52	3.10
5 yrs	**1.39**	**1.20**	**1.61**	1.08	0.95	1.21	**1.57**	**1.21**	**2.01**	**1.40**	**1.03**	**1.86**	1.46	0.53	3.17
10 yrs	**1.36**	**1.16**	**1.58**	1.08	0.95	1.23	**1.61**	**1.24**	**2.07**	1.34	0.97	1.81	1.53	0.56	3.32
15 yrs	**1.32**	**1.12**	**1.54**	1.10	0.96	1.25	**1.66**	**1.26**	**2.15**	**1.40**	**1.00**	**1.91**	1.38	0.45	3.22
20 yrs	**1.27**	**1.05**	**1.51**	1.10	0.95	1.27	**1.78**	**1.33**	**2.33**	1.40	0.96	1.97	1.62	0.53	3.79

Note: Indirect standardisation to Australian population, person years analysis, confidence intervals determined by Poisson regression. 10 year exposure lag.
Significant results highlighted.

4.4.8 Leukaemia

There were a total of 14 deaths from leukaemia during the study period, 4 lymphocytic and 10 myeloid. All deaths bar one occurred after 1980. All subjects worked during the period of modern chemical usage and 5 dippers worked in the DDT period as well.

Data on mortality rates for specific types of leukaemia within the Australian population is only available from 1983. However, data on leukaemia as a whole is available for the total study period, and this was used to calculate Standardised Mortality Ratios.

Seven deaths from leukaemia were identified in Dippers who had passed the 10 year exposure lag when approximately 4 would have been expected. This increase was not significant (SMR 1.77; 95% CI 0.71-3.65). There were similar, non-significant increases in mortality for controls and Dippers not yet past the exposure lag. Changing the exposure lag in this analysis had little effect on estimates or confidence intervals (Table 4-51).

Table 4-51 Standardised Mortality Ratios for leukaemia in subjects working during any chemical period: effect of different exposure lags

Lag	OBS	EXP	SMR	LCI	UCI
0	7	3.92	1.78	0.72	3.68
5 years	6	3.68	1.63	0.60	3.55
10 years	6	3.36	1.79	0.66	3.89
15 years	5	2.96	1.69	0.55	3.94
20 years	5	2.46	2.04	0.66	4.75

There were no significant increases in mortality for any chemical period or exposure category, although the greatest increase in mortality was for subjects working during the modern chemical period (SMR 3.70; 95%CI 0.76, 10.81). As described above, analysis of the modern chemical period excluded subjects who had worked at other times in the study. When subjects who had also worked prior to the modern chemical period were included in this analysis (Table 4-52), this increase became smaller and of borderline significance (SMR 2.61; 95% CI 0.96-5.68).

Table 4-52 SMRs for leukaemia in subjects working during the modern chemical period including those who also worked in earlier periods

DOSE	OBS	EXP	SMR	LCI	UCI
Controls	4	1.72	2.32	0.63	5.94
All	6	2.30	2.61	0.96	5.68
Dose0	1	1.61	0.62	0.02	3.46
Dose1	2	0.84	2.39	0.29	8.64
Dose2	3	1.15	2,62	0.54	7.64
Dose3	1	0.32	3.16	0.08	17.64

Changing the exposure lag for SMR analysis of leukaemia in the modern chemical period also influenced results (Table 4-53, Table 4-53). Under the zero lag model, the SMR for all Dippers working during the modern chemical period was of borderline significance (SMR 3.62; 95%CI 0.99, 9.26) and the SMR for the lowest exposure group of Dippers became statistically significant (SMR 6.41; 95%CI 1.32, 18.73).

Table 4-53 Effect of different lag periods on SMR analysis for leukaemia in the period of modern chemical use

DOSE	OBS	EXP	SMR	LCI	UCI
Lag 0 years					
All	4	1.11	3.62	0.99	9.26
1	3	0.47	**6.41**	**1.32**	**18.73**
2	0	0.51	0.00	0.00	5.90
3	1	0.13	7.68	0.19	42.77
Controls	3	1.13	2.67	0.55	7.79
Lag 5 years					
All	3	0.97	3.09	0.64	9.02
0	1	0.16	6.12	0.15	34.09
1	2	0.43	4.70	0.57	16.99
2	0	0.46	0.00	0.00	6.55
3	1	0.09	11.17	0.28	62.21
Controls	3	1.10	2.74	0.56	8.00

Mortality was also increased when deaths from the two main types of leukaemia combined were compared between Dippers and controls (Table 4-54) (SIR 1.24; 95% CI 0.36-4.29). This was greatest for those working in the modern chemical era (SIR 3.02; 95% CI 0.54-16.96), and for those working over 15 years this was statistically significant (27.44; 95% CI 2.23-337.99).

Table 4-54 Deaths in Dippers from all leukaemias compared to controls

	All Chemical Periods (1935-95)			Modern Chemical Period (1963-96)		
Dose	SIR	LCI	UCI	SIR	LCI	UCI
All	1.24	0.36	4.29	3.02	0.54	16.96
Dose1	1.34	0.26	6.96	3.33	0.52	21.38
Dose2	0.57	0.06	5.02	-	-	-
Dose3	2.06	0.43	9.92	**27.44**	**2.23**	**337.99**

Dippers also had increased mortality when deaths from specific types of leukaemia were compared to controls (Table 4-55). This was most marked for lymphocytic leukaemia during the modern chemical era, although the increase was not significant (SIR 6.81; 95% CI 0.30-156.85). When analysed by different exposure category, there was a significant increase in mortality from myeloid leukaemia among Dippers working over 15 years compared to controls (SIR 20.90; 95% CI 1.54-284.41). The wide confidence intervals around this estimate reflect the small number of deaths in this category (3 Dippers deaths, 2 control deaths).

Table 4-55 Mortality from Lymphocytic and Myeloid Leukaemia among Dippers Compared to Controls.

		All Chemical Periods (1935-95)			Arsenic Period (1935-55)			DDT Period (1955-62)			Modern Chemicals Period (1963-95)		
Condition	Dose	SIR	LCI	UCI	SIR	LCI	UCI	SIR	LCI	UCI	SIR	LCI	UCI
Lymphocytic Leukaemia													
	All	1.42	0.18	11.54	-	-	-	0.90	0.07	11.45	7.45	0.33	170.74
	Dose1	1.86	0.16	21.11	-	-	-	-	-	-	9.74	0.46	205.45
	Dose2	1.79	0.14	22.14	-	-	-	-	-	-	0.00	0.00	-
	Dose3	-	-	-	-	-	-				0.00	0.00	-
Myeloid Leukaemia													
	All	1.15	0.25	5.39	0.60	0.06	6.05	1.64	0.30	8.98	1.94	0.25	15.39
	Dose1	1.15	0.12	11.21	1.62	0.16	15.83	2.99	0.30	29.76	1.83	0.16	21.13
	Dose2	0.00	0.00	-	0.00	0.00	-	1.32	0.20	8.69	-	-	-
	Dose3	3.92	0.65	23.63	0.00	0.00	-				**20.90**	**1.54**	**284.41**

When subjects who had also worked in other periods were included in analysis of mortality of subjects working during the period of modern chemical use compared to controls, mortality remained raised but there were no exposure groups where this was statistically significant (Table 4-56). There was however an increase in SIR for increasing duration of exposure for almost all categories.

Table 4-56 SIRs for leukaemia among subjects working during the modern chemical period including subjects working in earlier periods

	Modern Chemical Period (1963-95)		
Dose	SIR	LCI	UCI
All Leukaemias			
All	2.75	0.79	9.62
Dose1	2.10	0.40	11.05
Dose2	3.19	0.69	14.63
Dose3	4.20	0.44	39.57
Lymphocytic Leukaemia			
All	3.21	0.39	26.57
Dose1	3.18	0.27	37.16
Dose2	3.88	0.29	52.62
Dose3	0.00	0.00	
Myeloid leukaemia			
All	2.52	0.53	11.93
Dose1	1.56	0.16	15.28
Dose2	2.80	0.43	18.24
Dose3	5.23	0.49	55.49

5 DISCUSSION

5.1 METHODOLOGY

As described in the literature review, much of the epidemiological research that has been undertaken into the potential health impacts of insecticides is hampered by methodological limitations. These include problems with exposure assessment, study size, length of follow-up, loss to follow-up, outcome ascertainment, comparison populations and lack of information on confounders.

By these standards, this study has a number of methodological strengths. These include the duration of follow-up, availability of alternative comparison populations and the comprehensive ascertainment of vital status and cause of death. The study also shares a number of the weaknesses of the research base upon which it is built, in particular in the area of exposure and confounder assessment.

5.1.1 Study design

The main body of this study comprised an historical cohort followed over 51 years from 1935 to 1996. The structure of this cohort was somewhat unusual in that it included exposed and control subcohorts. Most historical cohort studies identify controls from within the main cohort body, who have generally been assigned to a no exposure group based on historical exposure information.

The study subcohorts were defined from two different study populations. The exposed subcohort comprised field staff of the NSW Board of Tick Control, a group whose occupation involved almost daily exposure to a range of insecticides used over the study period. The control subcohort comprised outdoor staff from local councils in the same region, who might be expected to come from a similar section of the general population in terms of socio-economic status and lifestyle, but who would not be expected to have faced similar occupational insecticide exposures.

The purpose of this study design was to overcome some of the problems caused by the "healthy worker effect", where members of occupational cohorts are inherently healthier than the general community, thus making it harder to identify true increases in outcome when the general population is used as a comparison (McMichael, Andjelkovich et al. 1976). The control subcohort made it possible to compare outcomes directly between the exposed and control groups. If such a control group were, in fact, drawn from a similar population and shared similar lifestyles such as smoking behaviour, physical activity and diet, such a comparison would be inherently more "true" than one with the broader community.

Evidence on the comparability of the two groups comes from a number of sources. Firstly, there is a defensible logic behind selecting controls from outdoor workers in the same region. The general community in Australia is dominated by an urban base, where attitudes and behaviours are potentially quite different from the rurally based subjects of this study. Farm workers have been demonstrated in numerous studies to be intrinsically healthier than the general population (Blair, Zahm et al. 1992; Kristensen, Andersen et al. 1996), and it is possible the same may be true for other rural outdoor workers such as Dippers. While population mobility has increased over the past two decades, for the first forty years of this study the North Coast of NSW was a relatively isolated rural community, with poor transport links to other areas and a stable population with little inwards or outwards migration. There is little evidence available to compare lifestyles in this region with urban Australia during this period, but it can be expected that a range of lifestyle factors such as physical activity, diet and smoking might all be quite different from other parts of Australia.

Comparison of dates of birth and employment between the two groups shows Dippers tended to be born and commence employment about ten years earlier than controls (Table 4-1). These differences were statistically significant ($p<0.001$). However, both age and period of follow-up were adjusted for in the calculation of Standardised Mortality Ratios. When comparisons were made internally between the two groups, these were also adjusted for age and, where possible, period. Analysis was also often subdivided by period of chemical usage, when only subjects working during the same periods were compared.

One notable similarity between the subcohorts is the duration of employment (Controls 4616 days, Dippers 4453 days; p= 0.48), suggesting similar occupational patterns (Table 4-3). Loss to follow-up was also similar between the two groups despite the age differential (Dippers 7.25%, Controls 6.3%).

A further component of the study involved a survey of surviving members of each subcohort to collect information on a range of possible confounders and non-fatal outcomes. This information is subject to several major flaws discussed below, including response bias and difficulties extrapolating the behaviours of surviving subjects to that of subjects who had died, in some cases many years earlier. Nevertheless, it provides the opportunity to make some comparison between the lifestyles of surviving members of each subcohort.

This survey confirms that there was a clear difference in reported occupational use of pesticides between the two groups (OR 10.38; 95% CI 6.14-17.54). While there was a significant difference in years spent at school between the two groups (Table 4-6), this was only small in absolute terms (means of 8.7 years at school for Dippers and 9.1 years for controls). This would be expected since Dippers in the cohort were older than controls. Years at school was included in the survey as a surrogate measure for socio-economic status. The small difference in educational experience between the groups suggests there was little meaningful difference in socio-economic status. The survey also found that, after adjusting for age, there was no statistically significant difference in respondents from either group who reported ever having drunk alcohol (OR 1.45; 95% CI 0.84-2.51). These findings suggest the two groups were, in fact, drawn from similar social backgrounds.

However, the survey does suggest that past smoking may have been more prevalent among Dippers than the control group. Of respondents, 103 (20.1%) Controls and 64 (19.3%) Dippers reported being current smokers, while 218 (42.6%) controls and 173 (52.3%) Dippers reported being ex-smokers. After adjusting for age, there was no statistical difference between current smokers in each group (OR 1.20; 95% CI 0.83-1.73), Dippers, however, were significantly more likely to report ever having smoked (OR 1.66; 95% CI 1.21-2.28). The influence of smoking patterns on the study findings is discussed below.

In summary, while there appear to be some smoking differences between the exposed and control cohorts, it seems likely that the lifestyles of the two groups were reasonably similar. While there are also some analytical difficulties in comparing the two groups (see below), the availability of this second comparison group allows for a deeper interpretation of mortality patterns amongst Dippers.

Most other cohort studies examining the health impact of pesticides have been limited to comparison with the broader population, and have drawn controls internally. Exceptions include a study of pesticide exposed workers which was handicapped by a short follow-up period and potential reporting bias (Morgan, Lin et al. 1980), and a more recent study of aerial pesticide applicators (Cantor and Silberman 1999). In this latter study, significant differences were found in mortality from pancreatic cancer and leukaemia when applicators were compared to a control group of flight instructors. However, when mortality among applicators was compared to the U.S. population, no significant increase could be identified, and a significant decrease was found for leukaemia in controls. The authors suggest this, in part, reflects the innate health of pilots who are required to pass regular medical tests to retain their licences. They argue that the comparison between applicators and control pilots is more valid than with the general population. This may be particularly true for smoking related disease.

This is similar to the situation with farmers who are also believed to lead a healthier lifestyle than the general population. For either farmers or pilots, studies limited to a comparison with the general population will be biased towards a null finding.

However, comparisons to a control sub-cohort, as in our own study or the study of aerial applicators, also have methodological limitations. Most significantly, it is important that the exposed and control groups are truly comparable. As discussed above, for our study it seems reasonable to conclude that the exposed group has more in common with the control sub-cohort than with the general population. Comparison with this group would therefore be more likely to give a true estimate. However, another problem with comparison with a control group lies in statistical analysis, particularly of rarer conditions such as leukaemia where the

numbers used to determine the denominator in these calculations may be quite small. In these cases, the estimate does not necessarily have a low error variance and may reflect a random lower incidence in disease among controls. In the example of increased mortality from leukaemia among aerial applicators, this may simply reflect a reduced mortality among controls in an uncommon outcome (total 4 deaths). To allow for this sampling variability, confidence intervals for our study were calculated using likelihood ratio based methods, making it more difficult for such associations to be identified as significant.

As described below, our study has also chosen to take a weight of evidence approach, where information from both internal and external comparisons is considered when examining possible associations. This is supplemented by information collected from surviving cohort members. While each component of this analysis has its strengths and weaknesses, the total study approach provides a more complete package with which to assess possible associations. In particular, it allows us to examine the possible confounding effects of smoking and other lifestyle factors.

The cost of taking this broader approach is significant. Certainly, one of the more expensive components of this study was the follow-up of surviving cohort members. However, because it allows a much deeper examination of identified associations, this appears to be a worthwhile investment.

5.1.2 Exposure assessment

As outlined in the literature review, one of the common failings of much of the epidemiological research on pesticides is the lack of accurate data on subject exposure. In the absence of this information, many cohort studies have relied on occupational categorisation to indicate subjects likely to have experienced pesticide exposure. This approach potentially has several weaknesses, particularly if there is heterogeneity of exposure within categories.

This study also relies on occupational categorisation as a surrogate for exposure. However, the work practices of cattle dipping staff have a number of characteristics that suggest this is a reasonable approach. The main work of subjects in the exposed, Dipper, subcohort was insecticide application, minimising variation of exposure within this category. While there would have been some variation in behaviour between subjects and over different periods of time, there is considerable anecdotal evidence that their insecticide exposure was consistently high.

Some, very limited, direct measures of exposure are available on cohort members. Blood samples taken in the 1980's for serum organochlorine levels were available for 25 subjects: 14 controls and 11 Dippers (three of whom worked in the period when the organochlorine insecticide DDT was widely used). These samples were taken, approximately twenty years after use of DDT in the dipping program ceased. However, since DDT is a persistent chemical in the body, the results are a good indication of past exposure (Beard, Marshall et al. 2000). These results appear to confirm many of the exposure assumptions upon which analysis for the study was based. Firstly, they suggest that Dippers potentially faced extremely high exposures compared to other rural workers and the community as a whole. Mean DDT levels in exposed Dippers were over five times that of members of the control subcohort and eight times that of Dippers who did not work during the DDT era.

While there is a wide range in the results of biological monitoring (Table 3-6) in the three DDT exposed Dippers (10ppm, 28ppm, 80ppm), all were well above the means of the two non-occupationally exposed groups (Controls 6.7ppm; non exposed Dippers 4.25ppm). Thus, while it seems likely there was a wide range of exposures within the Dipper cohort, these results support the anecdotal evidence that exposure to insecticides in Dippers was also generally well above that in controls. While these results strictly apply only to Dippers working in the DDT chemical period, it seems reasonable to assume that Dippers in different chemical eras would also have faced similar high exposures to the chemicals they used. Anecdotal evidence from Dippers suggests that occupational hygiene practices changed little until the latter part of the study period, when subjects became more aware of the need to minimise exposure.

Biological monitoring of controls also supports the study assumption of little occupational exposure to DDT (and, by extrapolation, other insecticides) in this subcohort.

It is also worth noting that the mean serum total DDT results for Dippers not working in the DDT era were no higher than that for controls. One possible confounder of exposure categorisation by chemical period would be if site contamination from previous chemical usage resulted in Dipper exposure to chemicals no longer in use. For example, both arsenic and DDT are persistent in the environment, and soil contamination from past use or chemical discharge may present the opportunity for ongoing exposure after subjects were classified to a later chemical period.

However, compared to subject exposure to chemicals actively in use, exposure to contaminants is likely to be small. Both arsenic and DDT bind tightly to soil and are of very low volatility (Beard, Williams et al. 1992). Theoretical exposure routes to contaminated soil are therefore likely to be limited to the ingestion of contaminated soil or inhalation of contaminated dust. Even with high levels of contamination, such exposure is likely to be low in adult males (Beard 1993). The low mean serum DDT levels in non DDT exposed Dippers supports the assertion that site contamination is unlikely to have confounded the relationship between specific chemical periods and outcome.

In addition to categorising by exposure group (Dippers and controls) the study also uses duration of employment as a surrogate measure of exposure dose. The categories chosen were selected before analysis commenced to ensure the maximum number of subjects in each and to avoid investigator bias from choosing categories to maximise differences.

Estimation of a range of exposures is useful for a number of reasons. Perhaps most importantly, it allows exploration of dose-response patterns, which can support the argument for a causative relationship. However, for a number of reasons, absence of a dose-response pattern does not exclude a true causative association. For example, since different exposure sub groups may have intrinsically different population structures, this may influence the

results of studies such as this, which compare indirectly standardised risk ratios (Axelson and Steenland 1988).

Another potential problem derives from the use of duration of employment as a surrogate for exposure dose. Inherent to this approach is the assumption that exposure is consistent over the employment period. This may not be true. Less experienced workers may be given "dirtier" jobs or, through inexperience, may be more likely to inadvertently come into contact with the hazard of interest. Similarly, short-term employees may have had intensive exposures, although of short duration.

This study uses duration of employment not just as a surrogate for total exposure, but also as an indicator of exposure to different chemicals. It is unlikely that specific work practices during these periods were consistent. For example, when chemicals were phased out of action, staff were required to empty baths by hand, and dispose of the redundant chemical in holes dug adjacent to the Dip (Beard, Williams et al. 1992). Sludge left in the dip also needed to be scooped out before the new chemical could be mixed and added to the bath. This was therefore potentially a time of extremely high exposure, both to the chemical being replaced, and to the new insecticide as the bath was refilled. In 1962, for example, DDT was phased out across the quarantine area and this process would have been undertaken by staff repeatedly at approximately fifteen hundred dips. Subjects working for 1962 alone may therefore have faced even higher exposures to DDT than those working for the entire period 1956 to 1961.

Most Dippers in this study also faced multiple chemical exposures. Dippers were allocated to DDT and Arsenic periods even if they had also worked during periods of other chemical use. Thus, a single subject may be included in the analysis for both these periods. If an association is identified, it may therefore relate to the influence of more than one chemical. For example, a high rate of cancer during the DDT period may relate to subjects exposure to both DDT and arsenic, and not be evident, or evident to a lesser extent, if they had been exposed to only one or other chemical. In addition, the chemical periods themselves are somewhat arbitrary. DDT was phased in over about 5 years, although it was replaced over a relatively short period around 1962.

The study also generally aggregates all exposures since 1962 into a single chemical period, while excluding Dippers who also worked during earlier periods. A wide range of chemicals were used during this time, and anecdotal reports suggest Dippers would have faced many exposures. In one sense, this provides information from the "real" world where multiple exposures are widespread and allows for the effect of interaction between these chemicals. On the other hand, subject exposure during this period may have been very heterogeneous and this might have the effect in the analysis of masking the health impact of a particular chemical, since some subjects in the study group may have faced little or no exposure to it.

This may be particularly true for subjects working before or after 1976 when the chemicals used in dips changed considerably. Thus, while a Dipper working in either of these periods appears likely to have had some exposure to the full range of chemicals in use, subjects working exclusively before 1976 would have faced no exposure to chemicals used after that time and vice versa. Categorising these subjects in the same exposure group therefore tends to bias the study to the null. To overcome this bias, where raised mortality was identified for subjects working during the total modern chemical era, further analyses were undertaken narrowing the category to subjects working exclusively between 1963 and 1976. This also has the effect of narrowing the list of possible exposures associated with any identified outcome. Unfortunately, the follow-up period available to staff only working during the 1976-1996 period is too limited to allow meaningful analysis of mortality.

As described in the Methods section, no data was available for a number of subjects on either dates of commencement or completion of employment. These subjects were generally excluded from analysis by exposure group. However, to minimize the loss of useful information, these subjects were also given an estimated duration of employment calculated from the mean employment period for their group. For significant outcomes, further analysis was undertaken adding subjects with estimated durations of employment to the analysis. In almost all cases, addition of these subjects made little difference to the SIR or SMR or the associated confidence limits. This reflects the size and power of the study, even when limited to subjects with full data.

In summary, like most research in this field, this study incorporates little direct exposure measurement. It does, however, have several strengths. These include some limited biological monitoring of cohort members (which appears to support the approach taken to exposure categorisation), and the inclusion of a control subcohort for comparison.

Since the study covers several chemical periods, this also allows the examination of disease patterns with changing chemical use. It would be unlikely that all insecticides per se would cause the same adverse outcomes, and so discriminating between these periods may enable trends related to specific chemicals to become manifest. On the other hand, this form of exposure estimation is crude, and by aggregating the outcomes for subjects facing a range of different exposures, may mask real associations. In analysing the results of this study, it is therefore important to remember the implications of this method of exposure estimation.

5.1.3 Study size and follow-up

In comparison to other studies in this field, the exposed cohort in this study was reasonably large, and the potential follow-up period was notably long. Loss to follow-up (6.8 %) and failure to determine cause of death (2.7 %) were both above generally accepted targets (Checkoway, Pearce et al. 1989).

The relatively large size of the cohort and long follow-up period give the study considerable power to identify significant associations in common outcomes such as circulatory disease. When examining the total group of exposed workers, the study was able to detect raised SMRs of as low as 1.10 for all deaths (SMR 1.10; 95% CI 1.01-1.19), and 1.20 for common outcomes such as circulatory disease (SMR 1.20; 95% CI 1.02-1.39). On the other hand it was unable to confirm as significant an SMR of 3.00 for less common outcomes such as deaths from diabetes in the modern chemical period (SMR 3.00; 95% CI 0.97-7.00).

For common conditions, the power of the study to identify a significant difference in mortality between the exposed and controls groups was similar to that for SMR estimation. However,

for uncommon outcomes this fell markedly, so that an SIR of 4.71 for diabetes over the modern chemical era could not be confirmed as significant (SIR 4.71; 95% CI 0.50-44.44). The power was smaller again for the DDT and arsenic periods when subject numbers were smaller (although to some extent this was balanced by longer follow-up periods).

5.1.4 Possible study bias and confounding

Considerable effort was made throughout the study to avoid possible sources of bias.

To minimize selection bias, subjects were only included during the cohort enumeration if their details were identified from government records. A number of other potential cohort members who had been identified by the recall of other staff or because of a noteworthy outcome but who did not meet these selection criteria were excluded. Selection of controls was limited to Councils responding from within the tick quarantine area.

To ensure investigator bias was minimised, key analytical criteria were set before the analysis commenced. These were then followed throughout analysis, with variations from this methodology reported by exception. These criteria included:

- Exclusion of females and subjects with unknown date of birth;
- Exposure lag of 10 years;
- Duration of exposure groupings;
- Exclusion of subjects with incomplete employment information from analysis by exposure group;
- Definition of insecticide exposure periods;
- Exclusion of subjects working during other periods in analysis of the modern chemical period and inclusion of subjects working during other periods in analysis of the DDT and arsenic periods.

Matching of subjects with national and state registries was also undertaken in a standardised way using preset algorithms and blinded staff to minimise bias (see below). Where matching

was uncertain, matches were rejected. This may have led to a slight bias to the null, as would the inevitable missed matches.

Bias from loss-to follow-up is unlikely to be high as vital status ascertainment for the study is estimated at 93.2%, a figure considered acceptable in large cohort studies.(Checkoway, Pearce et al. 1989) Cause-of-death determination rate for the period 1983-1996 was over 98%, well above the desirable target set by the same authors of 90-95%. Loss to follow-up in exposed subjects (7.25%) was slightly higher than in controls (6.3%) but this probably largely reflects the age differential between these sub cohorts and is unlikely to have influenced the study findings.

Confounding by age and period of follow-up were generally controlled for in analysis. Calculations of Standardised Mortality Rates were based on a person-years analysis, stratified by age and period. For common diseases, calculation of Standardised Incidence Ratios (SIRs) were adjusted for log age and period (crudely defined as before or after 1960). Because of the limitations of small numbers in both numerator and denominator, it was not possible to adjust for period when calculating SIRs for less common outcomes. However, for most of these outcomes, univariate analysis failed to identify significant association with period of employment, suggesting this was unlikely to bias results.

Confounding by smoking may have influenced the study findings and is discussed below.

As discussed above it is also possible for the study to have been confounded by the "healthy worker effect" or by differing lifestyles between the exposed group and the general community. It was for this reason that a control subcohort, drawn from as similar a population as possible, was included in the study. This allows examination of the extent of the potential for bias from these two influences.

5.1.5 Survey of Surviving Cohort Members

The most serious potential sources of bias in this study relate to the survey of surviving cohort members. The response rate to this survey was only 54.9%, and Dippers (60.9%) were significantly more likely to respond than controls (51.6%) after stratifying the cohort into 5-year age groups. However, the percentage of Dippers and controls choosing to return a blank questionnaire was almost identical.

The low response rate for the survey probably largely reflects outdated addresses in the main study database. A small team of staff was recruited to follow up non-responders and attempts were made to contact them by telephone to encourage them to complete and return the questionnaire. Unfortunately, complete contact records have been lost, but anecdotal reports suggest most subjects contacted ultimately responded. A large number of subjects could not be contacted by phone and presumably had changed address.

If the response rate was due to factors other than failure to make contact, this introduces several opportunities for recruitment bias. For example, it might be possible that subjects with an illness may have been more or less likely to respond than those without. However, the main purpose of the survey was not to estimate the prevalence of outcomes or behaviours (apart from smoking behaviours) or to compare these estimates with the broader community. Rather, the survey was intended to compare the prevalence of outcomes between the Dipper and control subcohorts. Differential response due to illness, or some other factor, would influence the study findings only if these factors were not evenly distributed between the groups.

However, if the increased response rate among Dippers also reflected underlying differences in self reporting patterns between the two sub cohorts, this may influence the comparison of disease prevalence between the two groups. The social environment within which the study took place may have been conducive for such a tendency. Several workers compensation claims against the Board of Tick Control were outstanding at the time of the study, and it is possible that Dippers might have seen this as an opportunity to further their interests. On the other hand it is also possible that because their health had become a prominent issue and

featured on a television documentary some years before (see Introduction), Dippers may have taken more time over their responses in an effort to identify potential causes of this reported ill health. In either case, responding Dippers may have been more likely to report adverse outcomes. Higher rates of disease in Dippers may thus reflect underlying bias rather than true increases in prevalence. This possibility needs to be considered when assessing the validity of results.

If a systematic reporting bias were influencing the study findings, it might be expected that this would be consistent across the wide range of outcomes investigated. It is somewhat reassuring therefore, that a large number of outcomes were, in fact, reported less frequently by Dippers. It is also reassuring that many of the diseases reported more frequently by surviving Dippers were also identified as increased causes of death among Dippers both when compared to the control sub cohort and the broader Australian community. Identification of increases in both morbidity and mortality from these independent sources provides convincing evidence for a true association. Nevertheless, the potential for reporting bias needs to be borne in mind when considering results of this survey. This may be particularly true for vaguer outcomes such as ill-defined chronic disease.

Several strategies were put in place to minimise these potential sources of response and reporting bias. In all correspondence and when contacted in person, subjects were always advised the study was of outdoor workers rather than of cattle dipping staff, and that the impacts of a range of possible work practices were being examined. This served to minimize the expectation that the study might relate to factors relating to only one of the subcohorts. When the study was reported on the local media, this approach was also emphasised. Staff following up non-responders were also advised that the purpose of the study was to investigate outdoor workers, and were also kept blind to subjects' occupational category.

To maximise the response rate, considerable effort went into following up non-responders and this was generally done in the evenings to ensure employed subjects were not inadvertently excluded.

Nevertheless, there remains considerable scope for bias within this cross-sectional survey. For this reason, it has been used in the study more as an imperfect source of information on possible confounders (such as smoking), than as a truly representative picture of health outcomes. It has also proved useful to explore whether or not it provides support for associations suggested by the main part of the study. As discussed below, for two such outcomes (asthma and diabetes) the survey findings reinforce those in the main study.

The survey also identified increased rates of several potential non-fatal outcomes among exposed staff. Because of the potential bias involved in this part of the study, these need to be viewed with a degree of scepticism. However, these identified associations are useful for generating a number of hypotheses for future investigation.

5.1.6 Outcome ascertainment

The study used two approaches to determine subject outcome. Vital status was initially determined by matching the cohort with the Health Insurance Commission's Medicare database. Cause of death was identified by matching the cohort with the National Deaths Index (from 1980) and NSW and Queensland death registries (1945-82).

While there is no universal identification system in place in Australia, both the Medicare and deaths databases are comprehensive and well maintained by international standards (Kelman 2000) (Powers, Ball et al. 2000). One potential study weaknesses is the possibility of missed matches between these databases and the cohort. Before 1980, the study relied on staff at the NSW and Queensland Death Registries to match the cohort with the Registry databases. Since records before that time are not computerised, this required laborious hand matching and relied on the staff's expertise and experience.

Deaths after 1980, and enrolment on the Medicare database, were identified by complex computerised matching procedures. Even with these standardised approaches, the lack of an identifying reference for each individual meant the matching would not have been perfect. A

standardised algorithm was used by the study to ensure any bias in matching subjects was minimised, and the rigorous nature of this algorithm would have tended to exclude possible true matches rather than include false matches.

The accuracy of vital status and cause of death ascertainment can be demonstrated by examining the 337 subjects who were identified as having ceased Medicare enrolment after 1985. Death certificates were found for 328 of these subjects, leaving 9 lost to follow-up. These may represent subjects changing names, leaving the country or having died but not been matched with death registry notifications. The high percentage of death certificates matched for those having ended Medicare enrolment (97.3%) suggests the computerised matching process was remarkably accurate.

The rigorous application of matching algorithms would have made it more likely that matching errors resulted in missed rather than false matches. This approach underpins the accuracy of the results but would also have tended to bias the study to the null.

5.1.7 Analytical techniques

The analytical techniques used in this study generally take standard approaches to examination of this historical cohort. All analyses were undertaken using the SAS statistical package (SAS/STAT version 6.1. SAS Institute Inc.), apart from ANOVA calculations, which were undertaken using SPSS for Windows (Release 8.0.0, Copyright SPSS Inc., 1989-1997).

The person-years analysis is based on a program developed for SAS by Pearce and Checkoway ((Pearce and Checkoway 1987)). This model generates person-years data for each individual by considering each year of follow-up in turn and by creating a separate record with appropriate values for the variables year at risk, age at risk, length of follow-up (all in 10-year groupings) and duration of employment (1-4 groupings depending on the analysis). The program was also used to lag duration of employment levels by varying durations to allow for any potential latency period. The data generated by this program was then used to calculate Indirect Standardised Mortality Ratios by comparing the information on the cohort with age

and period stratified data on the Australian population using an accepted program by Daly ((Daly 1992)). Confidence intervals were calculated using Poisson regression.

One shortcoming with the person-years program was its management of control subjects. Since the program was designed to analyse a single cohort where controls were restricted to subjects not yet past the identified lag period, it had difficulty running the full person years stratification, including lag period, on the separate control sub cohort that was integral to this study. This problem was overcome by running the program separately for both Dippers and controls. This ensured the SMRs calculated for controls were derived by the same methodology as for the exposed subcohort.

A range of different exposure lag periods were applied for key outcomes. In general, apart from the extreme settings such as 0 lag years, the exact exposure lag interval chosen made little difference to either SMRs or confidence limits. As described in the Methods section, it was decided before data analysis commenced that an exposure lag period of 10 years would be incorporated into the model and this was maintained throughout the general analysis to avoid observer bias. For the one or two conditions where changing the lag did influence statistical significance, it should be borne in mind that this initial decision was somewhat arbitrary. As discussed below, this study has taken a weight of evidence approach to interpretation of results, and the impact of exposure lagging has been considered in this light, both in general, and for specific conditions.

Calculation of Standardised Incidence Ratios (SIRs) between the two subcohorts was somewhat more problematic as it needed to take account of the small number of cases that may be present in the denominator for less common conditions. In such cases the denominator estimate can no longer be assumed to be known without error. To take account of these issues, for this part of the analysis Poisson regression was used to calculate the estimate, and likelihood ratio based methods were used to define the confidence limits (Venzon and Moogavcar 1988). Nevertheless, for rare conditions, it is possible that high variance in the denominator might result in associations being identified when, in fact, they relate to an

unrepresentative low incidence identified in controls rather than a high incidence identified in Dippers.

Given the analytical difficulties inherent in calculating SIRs for uncommon outcomes, anomalous results in rare conditions need to be viewed with some skepticism unless there is supporting evidence from other analyses. In particular, there would generally need to be evidence of an increased SMR for the same condition, to be confident such a finding was not a result of a chance reduction in control deaths. Fortunately, in this study, there is little conflict between the two forms of analysis.

Outcome information from the cross-sectional survey was generally in the form of binomial variables and analysis was undertaken by logistic regression adjusted for log age and whether subjects had ever smoked. Where the outcome variable data were numeric (years at school and neuropsychological score), univariate analysis of variance was used in the SPSS statistical program. These are standard approaches to a relatively simple cross-sectional dataset.

More problematic in analyzing this survey is the opportunity for the influence of a range of possible biases (see above). These create the strong possibility of incorrectly identifying possible associations. While the analytical techniques applied to the survey data are straightforward, the quality of the data means results of the analysis need to be considered in light of the evidence available on cohort members from other sources.

5.1.8 Summary of methodological strengths and weaknesses

Compared to much of the epidemiological research undertaken in the field of pesticides, this study has a number of strengths. It is of reasonable size, with a long follow-up period for many subjects. Access to national databases ensures assessment of vital status and determination of cause of death is rigorous, while loss to follow-up is low.

The study design incorporates two control groups for comparison, providing the opportunity to evaluate the impact of potential confounders such as smoking. There is also limited information from biological monitoring to substantiate some of the exposure assumptions of

these groups. The range of insecticide exposures across the total study period also allows some investigation of the impact of specific chemicals, and provides opportunities to further examine the analytical results for consistency. Despite its limitations, the cross-sectional survey of surviving cohort members provides further information on possible confounding and allows the prevalence of non-fatal outcomes to be compared with mortality for consistency.

There are few published studies of this scope and comprehensiveness.

Unfortunately, the study also shares some of the significant methodological problems faced by others in the field, most notably around assessment of exposure. Like much epidemiological research on pesticides, subjects have been assigned an exposure category based on their occupation. This approach carries an inherent potential for misclassification and consequent bias toward the null. In this study, there is a relatively low likelihood of misclassification of subjects' exposure to insecticides *as a group* since there is strong anecdotal evidence, supported by limited biological monitoring, to suggest that almost all dipping staff faced recurrent high exposures to the particular insecticides in use at any one time.

However, it is unlikely that all insecticides share the same potential for adversely influencing human health. Different pesticides have different modes of action and are metabolized by different metabolic pathways. Department of Agriculture records indicate that, throughout the study period there were generally two or three chemicals being used concurrently at different dips. Staff duties usually required exposed subjects to work at a number of dips, and Dippers may therefore have been exposed to a number of different chemicals over any specific period of time. However it is likely that some may in fact have faced minimal exposure, or not have been exposed at all, to specific chemicals during this period. If these were the chemicals responsible for a particular outcome, misclassifying these subjects as exposed would serve to bias the findings to the null and mask the impact of exposure. For example, if there was an actual trebling of mortality in subjects exposed to a particular chemical but it was only used by half the Dippers working during a particular period of chemical use, the SMR identified for the study would have been only twice that expected.

This is particularly relevant for the period of modern chemical use, when a large number of different chemicals were used at different times. Most importantly, there was a significant change in chemicals used around 1976 (Table 3-5). Including subjects working exclusively before this time with those working after 1976 may have the effect of masking the impact of a specific chemical on health status. This would probably be most evident in subjects working for shorter durations, who would have been less likely to work in both of the modern chemical periods.

For these reasons of exposure misclassification, it is likely there is a tendency within this study to bias findings toward a null result, and non-significant findings should not be seen as definitive indications of chemical safety.

On the other hand, this study investigates a large number of outcomes and it is possible that just by chance some "significant" associations may be identified. All positive findings need to be considered with this potential in mind.

5.2 STUDY FINDINGS – OUTCOMES

Throughout this study, 95% confidence intervals have been used to assess statistical significance. A number of significant associations were identified during analysis. Mortality was also increased for a number of other outcomes, but not to the degree this increase was statistically significant. Many of these increases may have been due to chance variation in mortality patterns. However, it is possible that others represented a real increase among exposed subjects, and that failure to identify these patterns as significant reflected lack of statistical study power. A number of methodological problems outlined above also tend to bias results to such a null finding.

On the other hand, more than 20 different outcomes were examined in the analysis, over three different study periods, in two subcohorts, one of which was often divided into three or four categories by duration of employment. In such a large number of separate analyses, it would

be anticipated that some statistically significant associations might be identified just by chance.

Judging whether a statistically significant finding might be merely the result of multiple comparisons, or whether a non significant increase in mortality may represent a true effect of exposure masked by a form of bias or lack of study power, requires a balanced approach to interpretation that considers all these possible influences.

In an attempt to achieve such a balance, rather than applying a rigid interpretation of statistical significance to the large amount of analytical output available, this discussion will explore disease patterns and assess the significance of possible associations in light of the total weight of evidence available. A number of possible factors may influence this assessment including the size of the association, the number of subjects involved, trends in other exposure categories, evidence from other research and whether the identified association is physiologically plausible.

As mentioned above, because of the multiple comparisons that are central to the analysis, there is an intrinsic risk that the study will identify some random increases or falls in mortality as significant. A number of possible approaches have been suggested to this problem. In this study, where so many other factors also influence the calculated estimates, the rigid mathematical approach recommended by some authors (for example widening the confidence interval beyond 95%) did not seem appropriate. Instead, as described above, a weight-of-evidence approach has been adopted, with no single result necessarily being accepted as clear evidence for or against a putative association.

Several of the identified associations occurred in less common causes of mortality. For these outcomes, in particular, other evidence supporting an identified association needs to be available to feel confident the finding reflects a real effect of exposure. Interestingly, however, no statistically significant decrease in mortality was identified in either exposed or control subjects.

Finally, when taking this weight-of-evidence approach, it is important to remember the relationship that many of these associations have to each other. For example, increased mortality in a particular condition over the total study period is not independent of an increase of the same condition identified in a specific exposure group during a particular chemical period. These are both reflections of the same finding, although knowing the period or exposure group in which it occurred may add information.

Similarly, an elevated SIR for a particular outcome that mirrors an elevated SMR for the same outcome in the same exposure group does not provide totally independent evidence supporting the identified increased mortality. However, since the internal control group is an alternative comparison population, and may be more likely to share certain behaviours such as smoking and employment status with the exposed group, it does lend confidence that the association persists after some allowance is made for possible confounding by these factors.

5.2.1 All cause mortality

As described above, when all cause mortality was compared with the Australian population, there were approximately 54 more deaths in Dippers than expected over the total study period. Dippers as a whole had a significantly elevated mortality, and there was also significantly elevated mortality in those working more than 15 years. The biggest increase in death rates compared to the Australian population was in Dippers working in the modern chemical era, and this appeared to increase with increasing duration of employment.

As discussed below, the main reasons for the increase in overall mortality are relatively small increases in SMR in common diseases traditionally linked with smoking. These included circulatory disease (29 excess deaths), respiratory disease (27 excess deaths), and total cancers (21 excess deaths) including lung cancer (12 excess deaths). Death rates for these diseases (and total mortality) also tended to be increased in controls.

While this study also identifies a number of larger increases in SMR for other outcomes, since these occurred in less common diseases their impact on total mortality rates is small. Higher

overall mortality is somewhat surprising given the general experience in occupational studies of a healthy worker effect, sometimes amplified in studies on pesticides by the healthier lifestyles of farmers (Alberghini, Luberto et al. 1991; Morrison, Semenciw et al. 1992; Kristensen, Andersen et al. 1996).

Two methodological factors may help explain the apparent minimal influence of this effect. Firstly, in this study, matching with deaths registers appears to have been very effective, minimising a bias towards underestimation from missed matches that may have been prevalent in other studies. Secondly, the long follow-up period for the study and 10 year exposure lag may have overwhelmed the impact of the healthy worker effect. This reflects evidence that the healthy worker effect is most marked during the period immediately after employment and may almost disappear after 15 years of follow-up (Checkoway, Pearce et al. 1989). The mean duration of follow-up in this study is over 20 years. Nevertheless, the healthy worker effect is still likely to have had some effect on the findings of this study, with the result that mortality, though increased, may have generally been slightly underestimated.

Finally, it appears that the lifestyles of the outdoor workers involved in this study did not follow the general trend identified in other research for farmers and other agricultural staff to have lower rates of smoking and smoking related disease. This is discussed below.

5.2.2 Cancer mortality

There was an increase in total cancer mortality of borderline statistical significance for Dippers as a group when compared to the Australian population, with the highest SMRs being in the modern chemical era. This reflects an additional 21 cancer deaths over the total study period. There were 12 excess deaths from lung cancer.

No Dipper exposure group or period had increases in SMRs for total cancers that were statistically significant. Similar increases in cancer mortality were also seen for both controls and Dippers not yet past the 10 year exposure lag. The increased cancer mortality among

controls during the modern chemical era was statistically significant (SMR 1.53; 95% CI 1.10-2.06).

Dippers only had a small, non-significant, increase in total cancer mortality when compared with controls. This increase was greatest in subjects working more than 15 years and the increase in mortality among this exposure group was statistically significant for both the total study period and the modern chemical era.

The only specific cancer with a significantly increased SMR in any exposure group or chemical period was pancreatic cancer in DDT exposed subjects working for less than 3 years (SMR 5.27; 95% CI 1.09-15.40). Mortality from pancreatic cancer was also increased when this same exposure subgroup was compared with controls. Pancreatic cancer is discussed separately below.

When subjects were grouped into Dippers, controls, and Dippers not yet past the 10 year exposure lag and compared with the general Australian population for the total study period, the only cancer with an SMR greater than 2 was bladder cancer in both council controls (SMR 2.12; 95% CI 0.58-5.42) and Dipper controls (SMR 6.62; 95% CI 0.80-23.91). Bladder cancer is known to be smoking related. A number of other cancers had SMRs above 2 in different exposure groups or periods, but only lung cancer in subjects working for over 3 years in the DDT period (SMR 1.45; 95% CI 0.97-1.45) and prostate cancer in the arsenic period (SMR 3.38; 95% CI 0.92-8.66) had lower confidence intervals approaching unity.

When Dippers were compared with controls, mortality from myeloid leukaemia was significantly increased for those working for over 15 years in the modern era. This, too, is discussed below.

Dippers also had increased mortality from several other cancers when compared with controls, although none were statistically significant. SIRs greater than 2.0, included brain cancer, rectal cancer and stomach cancer. The increase for lung cancer was only small (SIR 1.15;

95% CI 0.72-1.83), but in absolute terms this condition would have made the greatest contribution to the increased cancer mortality identified among Dippers.

These patterns of disease, and the identified increases in total cancer mortality appear to be strongly influenced by smoking behaviours in the Dipper and control subcohorts, which are discussed below.

Deaths from **Non Hodgkin's Lymphoma** (NHL) were raised for Dippers across the study period (SMR 1.64; 95% CI 0.6-3.57). Mortality among controls was less than expected (SMR 0.45; 95% CI 0.01-2.49) and when Dippers were compared with controls the Standardised Incidence Ratio was increased (SIR 4.57; 95% CI 0.53-39.39). While the default analysis failed to identify an increase in mortality among Dippers working exclusively during the period of modern chemical use (SMR 1.04; 95% CI 0.03-5.81), when subjects who had also worked in other periods were included, both the SMR and lower confidence limit increased (SMR 2.22; 95% CI 0.72-5.18). When NHL mortality among this same exposure group was compared to controls, the increase in Standardized Incidence Ratio for all exposed subjects was of borderline significance (SIR 8.71; 95% CI 0.97-78.12) and this was statistically significant for Dippers working between 5 and 15 years (SIR 11.60; 95% CI 1.11-121.74).

There were only six deaths from NHL in Dippers and one death among controls during the total study period. Since NHL mortality among controls was reduced compared to the Australian population, the raised SIRs reflect this low mortality in the comparison population. On the other hand, mortality among this group of Dippers was also raised compared to the Australian population and a dose response gradient was evident (Table 4-30).

As described in methodology, the decision to use the default analytical model was made before analysis commenced, and analysis of subjects working during the "modern chemical period" was limited to those only working during this time as there were adequate numbers for analysis and to try to limit the possible exposures that might be responsible for mortality variations. There is no intrinsic physiological reason why subjects working during earlier periods should be excluded and including them increases the study power. Nevertheless, the

large number of outcomes examined in this study risks identifying relationships that are not real simply because of multiple comparisons. This risk is amplified if associations are identified by the ad hoc addition of analytical models. For this reason and because control estimates rely on a single death, these findings need to be viewed with scepticism.

They are, however, consistent with a number of other studies that have identified a possible relationship between pesticides and Non-Hodgkin's Lymphoma. Implicated exposures include phenoxy acid herbicides (Hardell, Eriksson et al. 1981), DDT (Woods, Polissar et al. 1987) (Baris, Zahm et al. 1998) and farm life in general (Zahm, Weisenburger et al. 1993). However, study findings are inconsistent, and a recent large case-control study using previously collected samples to estimate DDT exposure failed to find a significant increase in NHL among subjects with high DDT exposure (Rothman, Cantor et al. 1997).

One possible explanation for the suggested relationship between a number of pesticides and NHL relates to immunosuppression (Vineis, D'Amore et al. 1992). NHL may be caused by common viruses that induce proliferation and immortalization of B-cells, followed by T-cell impairment. Pesticides and chlorinated solvents may also induce impairment or suppression of cell-mediated immunity. In this study such an effect may be further influenced by chronic exposure to bovine viruses.

Unfortunately, this study does not have the power to clarify the conflicting information currently available on NHL. While its findings are not inconsistent with a causative relationship between insecticide exposure and NHL, they may also be the result of the methodological issues discussed above.

Of the other cancers with higher than expected mortality, deaths from **prostate cancer** were increased in a number of exposure or period subgroups when Dippers are compared to the general population. While there was also a small overall increase in mortality from prostatic cancer when Dippers are compared to controls, this was limited to subjects working during the arsenic period. For the rest of the study period, mortality was almost identical in Dippers and controls. There also does not appear to be any pattern of mortality with different chemical

use, nor any clear dose response relationship. There is limited evidence from other studies of a relationship between pesticides and prostate cancer. If the standardised incidence ratio identified by one large recent study (SIR 1.13; 95%CI1.02, 1.24) is correct, then our own study would not have the power to identify such a small increase (Dich and Wiklund 1998). The literature review included in that study also identified 7 case control studies of prostate cancer where occupational analysis included farming or forestry. Only one showed a significantly elevated odds ratio. The results from our own research provide little clear evidence for or against such a relationship.

Another cancer showing non-significant increases in mortality among exposed subjects is **rectal cancer**. This increase is evident when exposed subjects are compared both to controls, and to the broader population. When compared to the Australian population, there was also a slight overall increase in mortality among controls, in particular during the modern chemical period, but not in Dippers not yet past the 10 year exposure lag, although only 0.58 of a death was expected in this latter group. SMRs for rectal cancer in exposed subjects are raised above two in exposure subgroups of all chemical periods. The spread of raised SMRs across different periods of the study argues against these findings being the result of exposure to a particular chemical.

The study also found an overall decrease in mortality from colon cancer in exposed subjects when compared to the Australian population. One alternate explanation may therefore be regional differences in death certificate reporting, with clinicians more likely to identify colorectal cancer as rectal than colonic. However, this decrease was also evident when exposed subjects were compared to controls and not evident when controls were compared to the Australian population. It is hard to understand why reporting would differ between exposed and control subjects.

Colorectal cancer is thought to relate partly to dietary patterns (Willett 2001), so it is also possible that increased mortality might represent dietary differences between exposed subjects and the Australian population. However, the increase in mortality among exposed subjects is

even more marked when they are compared with controls, and there is little reason to expect diet to differ markedly between the two subcohorts.

The evidence on rectal cancer generated from the study is therefore somewhat unclear. While, overall, the increase in mortality was neither large, nor significant (SMR 1.43; 95% CI 0.53-3.12), the findings are unlikely to be due to smoking, and are not inconsistent with the findings of some other studies suggesting a relationship between pesticides and colorectal cancer (Forastiere, Quercia et al. 1993; Zhong and Rafnsson 1996; Soliman, Smith et al. 1997).

There was a moderate but non-significant rise in mortality from **brain cancer** when Dippers were compared to controls, but there was a slight overall reduction when they were compared to the general community. Compared to the Australian population, there was a large increase in mortality among Dippers working for 5-15 years in the modern chemical era, but this was not as large as the increase seen in Dippers not yet past the 10 year exposure lag. However, these increases are the result of one death in the 5-15 years exposure group and two Dippers who died between 5 and 10 years after commencing work. For some exposures and cancer a latency period of less than 10 years may be more appropriate, so analysis was rerun for brain cancer using a 5 year exposure lag. Both the resulting SMR and SIR were high, but not statistically significant (SMR 3.03; 95% CI 0.62-8.84. SIR 4.70 95% CI 0.46-48.00).

When the number of cases involved is so small, even one or two random deaths can markedly change mortality estimates. Nevertheless, mortality from brain cancer across other chemical periods was low, and if a specific chemical in the modern chemical period was the factor causing this, its effect may be masked as not all exposed subjects may have been exposed (see discussion above). The excess in the modern chemical era is also not inconsistent with the results of several other cohort studies, which suggest a possible association with farming or pesticides (Morrison, Semenciw et al. 1992; Viel, Challier et al. 1998) (Figa-Talamanca, Mearelli et al. 1993). However, as concluded by one recent review, at present there appears to be inadequate existing data to confirm an association between exposure to pesticides and the subsequent development of brain tumours (Bohnen and Kurland 1995). This study provides little evidence one way or the other to further inform this debate.

5.2.3 Circulatory disease

Circulatory disease (ICD9 390-459) covers a wide range of outcomes including ischaemic heart disease, cerebrovascular accidents, aortic aneurysm and peripheral vascular disease. An interesting feature of this study is the consistently high reported mortality from ischaemic heart disease in controls and Dippers, but the more moderate increases identified for circulatory disease as a whole. An unlikely explanation might be that some exposure during this period altered the balance of disease presentation. However, the effect is not only seen in Dippers, but in controls and Dippers not yet over the exposure lag. It is also present across the range of chemical periods, making a single exposure an unlikely explanation.

When mortality from ischaemic heart disease is compared between Dippers and controls, the SIR is almost identical to that for circulatory disease. The most likely cause of this trend is regional differences in death certificate reporting, with local clinicians being more likely to identify death from myocardial infarction than other forms of circulatory disease. Since ischaemic heart disease can be considered as one of several manifestations of atherosclerosis captured under the coding for circulatory disease, total circulatory disease can probably be considered to better represent these mortality patterns and has been generally used in preference during the following discussion on smoking related disease.

5.2.4 Smoking related disease

This study identified increased mortality from a number of diseases known to be influenced by smoking and other lifestyle confounders, both in Dippers and controls and in a range of different exposure categories. While a number of authors have suggested that the potential confounding effect of smoking is modest unless the smoking habits of a study population are quite extreme (Axelson and Steenland 1988) (Blair, Steenland et al. 1988) (Blair, Hoar et al. 1985), it is important to determine whether the associations identified in this study may have been due to smoking patterns within the cohort rather than to insecticide exposure.

A number of methods have been proposed for control of smoking in epidemiological research (Axelson and Steenland 1988). Firstly, an analysis of all smoking related diseases in the study population may give an indication of the consistent influence that might be expected if smoking rates were high. Diseases classically associated with smoking include cancers of the lung, larynx, bladder, kidney, pancreas and oesophagus as well as respiratory and circulatory disease. In this study, there were too few cancers of the larynx (4), oesophagus (6) or kidney (3) for meaningful analysis. However, the overall SMRs in Dippers for all other smoking related diseases, excluding cancer of the bladder, were increased, suggesting smoking may have been responsible for some, if not all, of these findings (Table 5-1).

Table 5-1 Standardised mortality ratios (SMR) for key smoking related disease - all Dippers

	EXP	OBS	SMR	LCL	UCL
Circulatory Disease	280.38	309	1.10	0.98	1.23
Respiratory Disease	45.17	72	**1.59**	**1.25**	**2.01**
Lung Cancer	37.24	49	1.32	0.97	1.74
Pancreatic Cancer	5.86	8	1.36	0.59	2.69
Bladder Cancer	3.73	3	0.80	0.17	2.35

A second method for examining the influence of smoking related disease is to use an internal non-exposed subcohort. In this study, two non-exposed sub cohorts are available for comparison: Dippers who had commenced employment less than 10 years before the time of their death (i.e. had not yet passed the 10-year exposure lag period), and the control group of council workers. The overall SMRs for smoking related diseases in these control groups can be seen in Table 5-2. Deaths from all smoking related diseases apart from pancreatic cancer are increased in the Council Worker Controls. For both circulatory and respiratory disease, this increased mortality was statistically significant. In control Dippers, SMRs were increased for all except respiratory disease, although the numbers are small and none of these increases were statistically significant. These findings suggest that smoking also influenced mortality patterns in both control groups.

Table 5-2 Standardised mortality ratios (SMR) for key smoking related disease - all controls, Dippers in first 10 years of employment

	EXP	OBS	SMR	LCL	UCL
Council Worker Controls					
Circulatory Disease	138.01	165	1.20	1.02	1.39
Respiratory Disease	22.11	33	1.49	1.03	2.10
Lung Cancer	21.41	26	1.21	0.79	1.78
Pancreatic Cancer	3.30	2	0.61	0.07	2.19
Bladder Cancer	1.89	4	2.12	0.58	5.42
Non exposed Dippers					
Circulatory Disease	35.74	37	1.04	0.73	1.43
Respiratory Disease	4.48	3	0.67	0.14	1.96
Lung Cancer	3.96	7	1.77	0.71	3.64
Pancreatic Cancer	0.72	1	1.40	0.04	7.78
Bladder Cancer	0.30	2	6.62	0.80	23.91

Rates of smoking related disease in Dippers can also be compared with mortality in the control subcohort, which, as described above, was drawn from a population with similar social background (Table 5-3). When mortality in these two groups was compared, no Standardised Incidence Ratios were significantly raised for smoking related diseases. In general, SIRs also tend to be considerably lower than the SMRs calculated for each group in comparison with the Australian community. This is particularly evident for respiratory disease and lung cancer. On the other hand, mortality from pancreatic cancer was markedly more common in Dippers than controls (although this increase was also not statistically significant).

Table 5-3 Standardised incidence ratios (SIR) for key smoking related diseases

	SIR	LCL	UCL
Circulatory Disease	1.07	0.89	1.28
Respiratory Disease	1.22	0.81	1.86
Lung Cancer	1.15	0.72	1.83
Pancreatic Cancer	2.72	0.56	13.12
Bladder Cancer	0.40	0.09	1.84

These mortality patterns suggest there was some real variation in the mortality from smoking related disease experienced by the exposed and control subcohorts, with Dippers likely to have smoked more than controls. This difference was probably not great, as even with very

common diseases such as circulatory disease, the increase was not statistically significant. Even the upper bound estimate for circulatory disease, suggests an increase in mortality of less than 30%.

The conclusion that Dippers smoked slightly more than controls is supported by the self reported smoking behaviours of surviving cohort members. As described above, surviving Dipper cohort members who responded to a mailed questionnaire indicated similar age adjusted rates of current smoking (Odds Ratio 1.16; 95% CI 0.80-1.68), but significantly higher rates of past smoking than controls (Odds Ratio 1.66; 95% CI 1.21-2.28).

On the other hand, there are marked increases in smoking related disease for both groups when compared with the Australian community. The likely explanation is that smoking was considerably more common in both Dippers and controls than in the wider Australian population. Table 5-4 shows smoking patterns in surviving subjects responding to the study survey and compares them with results from an extensive telephone survey of male NSW residents taken in 1997-98 (Division 2000). In part, differences between sub cohorts and NSW residents relate to the age differences of the populations. When age adjusted current smoking rates among subjects responding to the survey of surviving cohort members was compared with the male NSW population, there was no significant difference either for Dippers (p=0.227) or controls (p=0.932).

Table 5-4 Smoking in Dipper, control and NSW male populations

	Dippers	Controls	NSW
Current smoker	64 (19.7%)	103 (20.1%)	26.7%
Ex smoker	173 (53.2%)	221 (43.2%)	27.6%
Never smoked	88 (27.1%)	188 (36.7%)	34.7%

However, the trends in smoking related disease identified in this study are more likely to relate to past smoking practices. Both Dippers and controls were more likely to report being an ex-smoker than the broader NSW community. Unfortunately, data from the NSW community for this category is not available by age, making comparison of age adjusted past smoking rates impossible. It should also be noted that these results represent the self reported behaviour of

survivors, which may differ markedly from cohort decedents from earlier years. However, these results suggest it is likely that both subcohorts had higher rates of past smoking than the general community.

The degree of potential confounding from smoking depends on the strength of its association with the disease in question. Thus, for lung cancer, moderate smokers are thought to have a tenfold risk for lung cancer, while heavy smokers have a twenty-fold risk. On the other hand, the risk ratio for bladder and pancreatic cancer from smoking is thought to be about 2-4, while cardiovascular deaths suggest about a 2.5 fold risk ratio for moderate smokers and 3.5 for heavy smokers (Axelson and Steenland 1988). Since the identified increase in mortality from pancreatic cancer for Dippers compared to the Australian population is far in excess of the increase in lung cancer or ischaemic heart disease, this increase is likely to be due to differences between the two groups other than smoking patterns. On the other hand, the relative size of the increases for lung cancer and circulatory disease are consistent with confounding from smoking.

In addition to the risk ratio for specific diseases, the influence of smoking on disease patterns depends on the relative smoking rates in the two populations being compared. When the known risk ratio for lung cancer was applied to differing Finnish working populations with known smoking habits (Asp 1984), the lung cancer mortality from smoking alone varied between 0.67 to 1.31 when compared to the total population composed of 24% non smokers, 28% exsmokers, and 48% smokers. The overall lung cancer SMR for Dippers in this cohort (SMR 1.32, 95% CI 0.97-1.74) is at the upper limit of this range.

Models have also been developed to predict the influence of different hypothetical smoking patterns on mortality rates. An increased risk ratio for lung cancer mortality of 1.33 has been suggested as the equivalent of a study population with approximately 35% non-smokers, 47% moderate smokers and 18% heavy smokers compared to a reference population with 50% non-smokers, 40% moderate smokers and 10% heavy smokers (Axelson and Steenland 1988).

The evidence for the likely influence of smoking on mortality in this cohort is therefore fairly consistent. The evidence from disease patterns suggests that both Dippers and controls smoked considerably more than the Australian population. Smoking related disease is also increased when Dippers were compared to controls, although to a lesser extent. The available self reported evidence from surviving subjects also suggests that Dippers smoked more in the past than controls, although current smoking behaviour was similar when adjusted for age. It therefore appears that, while both groups smoked more than the general community, this was somewhat more marked in Dippers than controls. Analysis of mortality in this cohort should be interpreted in light of these likely smoking patterns.

Regardless, for lung cancer, risk ratios for the exposure of more than 1.5 or 2.0 are unlikely to depend on uncontrolled confounding from smoking. For diseases less related to smoking, even smaller excesses are unlikely to be the result of confounding by smoking (Axelson and Steenland 1988).

5.2.5 Pancreatic cancer

Mortality rates from pancreatic cancer were raised for Dippers as a group when compared with both the Australian population and with controls, although neither increase was statistically significant. This high mortality was not shared by controls or by those Dippers not yet over the exposure lag, suggesting it was not related to underlying lifestyle differences with the Australian population. The degree of increased mortality was also considerably beyond that which would be expected from confounding by smoking. In comparison with both the Australian and control populations there was a marked increase in mortality with increasing duration of employment, suggesting a possible dose response relationship.

All Dippers dying from pancreatic cancer worked during the period of DDT use, and mortality during this period was also elevated compared to the Australian population and controls. For Dippers working less than 3 years, this increase was statistically significant in comparison with both controls and the Australian population. While Dippers working during the arsenic

era also showed a (non-significant) increase in mortality from pancreatic cancer, this might reflect the fact that all these subjects also worked during the DDT period.

Similarly, while there appears at first glance to be a convincing dose response relationship for mortality from pancreatic cancer in all Dippers, this may, in fact, merely be due to the greater chance of a Dipper having worked in the DDT period as the time they spent on the program increased.

In this study, the DDT period was defined as 1955-62 inclusive. However, as discussed in results, DDT was only introduced slowly into the dipping program and, while it was first used in 1955, it was not until 1961 that it appears to have been used in the majority of dips. This may have resulted in misclassification bias towards the null as, in the early years of the "DDT period", many Dippers may have only used DDT infrequently, while others may not have used DDT at all. If there was a true association between DDT exposure and pancreatic cancer, it might therefore be expected that this relationship would be stronger for Dippers working in the later years of the DDT era, when exposure to the chemical was more likely. Indeed, Dippers working during 1961 and 1962 show both increased standardised mortality rates and increasing lower confidence limits. The SMR, however, still remains just short of statistical significance.

The significant association identified within one of the Dipper subgroups, the fact this is present in comparisons with both the Australian and the control communities, the size of the increase and the trend for increasing SMR in the period of most likely DDT use are all consistent with a causative association between DDT exposure and increased mortality from pancreatic cancer.

These findings are also consistent with the results of other studies, although as described in the literature review, there is still no general agreement on whether pesticides as a whole, or DDT in particular, are associated with increased mortality from pancreatic cancer.

A recent large prospective study of lifestyle factors and pancreatic cancer followed 63,374 Norwegians over 12 years (Lund Nilsen and Vatten 2000). This study confirmed the influence of smoking on pancreatic cancer and also identified a higher risk among men occupied in farming, agriculture or forestry (RR 2.1; 95% CI 1.1-4.0). Pesticides as a group have also been associated with pancreatic cancer in cohort studies in flour millers, although not generally among other cohort studies in farmers (Thomas, Krekel et al. 1985; Alavanja, Blair et al. 1990). Several case-control studies of variable quality have suggested farming (Forastiere, Quercia et al. 1993), or DDT (Fryzek, Garabrant et al. 1997) may be associated with pancreatic cancer.

An earlier investigation found increased mortality among 5886 chemical manufacturing workers (Garabrant, Held et al. 1992). A nested case-control study based on interviews with next of kin and examining written work records to determine chemical exposures found an association between occupational DDT exposure and pancreatic cancer (RR 4.8; 95% CI 1.3-17.6). The risk increased with increasing exposure and was not appreciably altered when the analysis controlled for smoking (and other potential confounders).

However, other recent case-control studies have failed to find an association with insecticides (Bu-Tian, Silverman et al. 2001)or serum DDE levels (Hoppin, Tolbert et al. 2000). An ecological study of average serum DDE level by sample size, race and state also failed to find an association with pancreatic cancer (Cocco, Kazerouni et al. 2000).

One possible explanation for a relationship between pesticide exposure and pancreatic cancer lies in modulation of oncogene expression. Individuals with pancreatic cancer have a high prevalence of K-*ras* mutations in codon 12. A recent study measured concentrations of organochlorine compounds in serum taken at diagnosis in 51 subjects with pancreatic cancer and compared them to 26 hospital recruited controls (Porta, Malats et al. 1999). Cases with K-*ras* mutations had significantly higher concentrations of DDT and DDE than cases with wild-type K-*ras* after adjusting for lipids (p= 0.02). Serum concentrations of DDT and DDE were also significantly higher in cases than controls, although concentrations in cases with wild-type K-*ras* were similar to controls.

These results do not necessarily imply that organochlorines play a direct part in activation of K-*ras*. Rather, the compounds might enhance the effects of K-ras mutations or might provide a growth advantage to the mutated cells, for example through its actions as an endocrine disrupter. The results might also reflect the activation of some carcinogen promoted by DDT analogues, for example through induction of P450 enzymes in the liver. However, these recent findings on possible gene-environment interaction do lend a physiological plausibility to the association between DDT and pancreatic cancer identified in this study.

5.2.6 Leukaemia

Comparison of cohort mortality from leukaemia with the Australian population is limited by the unavailability of Australian data on specific leukaemia types for the majority of the study period. The two main forms of leukaemia, lymphocytic and myeloid, may be thought of as different diseases and are best examined separately. If a toxic agent such as an insecticide only exerted its effect on a specific form of this disease, aggregating this information would make it more difficult to identify a real relationship.

This study did identify a non-significant increase in all leukaemia mortality when Dippers who had passed the 10 year exposure lag were compared to the Australian population (SMR 1.77; 95% CI 0.71-3.65). There were similar, non-significant increases in mortality for controls (SMR 1.76; 95% CI 0.48-4.50) and Dippers not yet past the exposure lag (SMR 1.49; 95% CI 0.04-8.29). There were no significant increases in mortality for any chemical period or exposure category, although the greatest increase in mortality was for Dippers working during the modern chemical period (SMR 3.70; 95%CI 0.76, 10.81). There were a total of 2 deaths from lymphocytic leukaemia among Dippers working in the modern chemical era and 5 from myeloid leukaemia.

When subjects also working in other periods of chemical use were included in analysis of the modern chemical period, the SMR remained increased and this became of borderline significance (SMR 2.61; 95% CI 0.96-5.68). Similarly, when the default exposure lag period of ten years was reduced to zero, the increase in leukaemia mortality for subjects working only during the period of modern chemical use was also of borderline significance (SMR 3.62;

95%CI 0.99, 9.26), and the increase was statistically significant for subjects working less than 5 years (SMR 6.41; 95%CI 1.32, 18.73).

When mortality from leukaemia was compared between Dippers and controls, there was an increase of similar magnitude for Dippers as a group (SIR 1.24; 95% CI 0.36-4.29). This was greatest for those working in the modern chemical era (SIR 3.02; 95% CI 0.54-16.96), and for those working over 15 years this was statistically significant (27.44; 95% CI 2.23-337.99).

When, mortality among Dippers from specific types of leukaemia was compared to controls, there was also increased mortality for both lymphocytic and myeloid leukaemia. This increase was greatest for lymphocytic leukaemia, and was most marked for subjects working in the modern chemical era. There was a statistically significant increase in mortality from myeloid leukaemia among Dippers working more than 15 years when compared to controls (SIR 20.90; 95% CI 1.54-284.41).

These findings are based on a small number of events in each category and may simply reflect the multiple comparisons undertaken during analysis. Nevertheless, an increase in mortality from leukaemia is identified when subjects working during the modern chemical era were compared to both controls and the broader Australian population. For some of the analytical models used, this increase is statistically significant, or of borderline significance in Dippers working during this period either as a group or in different exposure groups. There is also a suggestion of a dose response relationship, with a tendency for mortality to be higher in subjects working for longer terms during the period of modern chemical use (Table 4-56).

Both the consistency of the findings for internal and external comparisons, and the suggestion of increasing risk with increasing duration of employment support the argument that the identified increase in mortality from leukaemia is real. Since mortality for total leukaemias among controls working during the modern chemical period is increased compared to the Australian population, the high SIRs also do not appear to be an artefactual result of low mortality among controls.

On the other hand, mortality among Dippers not yet past the 10 year exposure lag is increased, suggesting a possible relationship with an exposure not related to occupation. An alternative explanation for the increase among these subjects is the effect of an agent with a short latency or induction period. If this were the case, reducing or removing the exposure lag in analysis might give a more accurate estimate of mortality. There is considerable physiological plausibility to reducing the exposure lag for conditions such as leukaemia which do not require the build up of large tumour mass or metastases to cause death. When the exposure lag is removed from analysis, the SMR for Dippers as a group increased slightly, and became of borderline significance for the modern chemical period. Dippers working for less than 5 years during the modern chemical period had a significantly increased mortality using this model.

Several epidemiological studies have suggested an association between pesticide exposure or farming and leukaemia (Blair and Thomas 1979; Brown, Blair et al. 1990; Pearce and Reif 1990; Viel and Richardson 1993; Kristensen, Andersen et al. 1996). However, increased mortality from leukaemia has also been identified in gardeners (Hansen, Hasle et al. 1992) and aerial pesticide applicators (Cantor and Booze 1991) suggesting the identified associations are not the result of other farm related exposures..

The findings in this study do not conflict with the possibility that insecticide exposure, or exposure to bovine viruses, may be associated with increased rates of both lymphocytic and myeloid leukaemias. Unfortunately, the power of the study is not great enough to either clearly confirm or refute this increase. If the identified increase were simply due to exposure to bovine viruses, it would be expected that mortality would be increased consistently across the study period. However, the increase in mortality from leukaemia across the different chemical periods is uneven, suggesting an effect independent of bovine exposure. Specifically, the temporal trends identified in this study suggest a relationship between increased leukaemia mortality and exposure to chemicals used in the modern chemical period.

The findings of this study are thus suggestive of a relationship between leukaemia and exposure to modern insecticides. However, the results are based on a very small number of deaths and need to be viewed with caution.

5.2.7 Asthma

Mortality from asthma was high in exposed subjects, both when compared to the Australian population and when compared to controls. This increase was significant when Dippers as a group were compared with the Australian population, both for the whole study period and for the period of modern chemical use. There was also a tendency for increasing mortality with increasing duration of employment during the modern chemical period, with Dippers working between 5 and 15 years having an SMR more than double that in the less than 5 years group. The increase in asthma mortality was also significant when subjects working only in the early part of the modern chemical period were considered (SMR 5.82; 95% CI 1.20-17.00). There were no deaths in Dippers not yet over the 10 year exposure lag, nor in the most exposed group (although only 0.02 deaths were expected in Dippers working over 15 years).

There was a smaller increase in mortality from asthma identified in controls, although this was not statistically significant. When Dippers were compared with controls, increases in mortality were also evident, although they were not statistically significant. Overall, Dippers had three times the mortality of controls after adjusting for age and these increases were greatest in the modern chemical period.

The general analytical model used in this study excluded subjects starting work before 1963 from analysis of the modern chemical period. This was designed to minimise the influence of previous occupational exposure, and to help get a clearer picture of the impact of chemicals still largely in use today. Large numbers of subjects working in this later part of the study meant this still allowed adequate power to identify most meaningful associations. When the analysis was rerun for subjects working in the modern era but including subjects who commenced work before 1963, mortality remained raised. These results also became more statistically significant, presumably reflecting the increased power associated with this larger study group. For the comparison between Dippers and controls, this meant that increased mortality in the 5-15 years exposure group became of borderline significance ($p= 0.07$).

A possible association between working as a Dipper and asthma is supported by the survey of surviving subjects. The survey found significantly higher self reported rates of asthma in Dippers, and also in Dippers' offspring after adjusting for age and smoking. Dippers also reported higher rates of dermatitis/eczema, an atopic complaint linked to asthma. The association with asthma generally held for most individual occupational pesticide exposures reported, and there was no obvious trend between them.

Smoking disparities between exposed and comparison groups may have influenced the increased mortality from asthma identified in this study. As discussed above, it is likely that smoking may have been higher in Dippers than in the rest of the community. However, confounding by smoking is unlikely to explain risk ratios above 1.5-2.0. The increased mortality identified in this study far exceeds these levels. Mortality in Dippers not yet past the exposure lag of 10 years was also not increased as might be expected if smoking was the cause of the excess mortality.

However, mortality from asthma was also increased slightly in controls. This may represent the impact of smoking, since other smoking related diseases were also high in this group. However, as discussed above, smoking related mortality was not significantly different between the Dippers and control groups, even for common outcomes such as circulatory disease. When asthma mortality in Dippers was compared with controls, there were large standardised incidence ratios, although these were not significant (for the modern chemical era SIR 4.38; 95% CI 0.42-45.78). Unfortunately, small numbers did not allow comparison in this period with different exposure subgroups. The persisting high SIR when Dippers were compared with controls supports the case for the identified increase in mortality being real and not simply smoking related.

This conclusion is also supported by the findings of one recent study that the prevalence of asthma in rural youth smokers was approximately double that in non-smokers (Omland, Sigsgaard et al. 1999). Since the difference in smoking patterns between exposed subjects and either the Australian community or the control subcohort is relative rather than absolute, the influence of smoking on the findings of this study is likely to be much lower. Smoking would

therefore not explain the size of the trends identified in this study. Survey responders also reported similar rates of current smoking.

The possibility that the increased asthma mortality identified among subjects is related to occupational exposure is also supported by the increase in self reported prevalence of asthma in Dippers compared to controls. While the shortcomings of this survey have been discussed above, the findings were adjusted for age and smoking status. Of the 6 associations identified as significant by logistic regression, 3 were related to asthma or atopy.

These findings are supported by a limited amount of evidence from other researchers.

A cross-sectional study of 1,939 male farmers (Senthilselvan, McDuffie et al. 1992) identified a significantly increased prevalence of asthma in subjects exposed to carbamates after adjusting for age, smoking pack-years, and nasal allergic reactions (OR 1.8, 95% CI 1.1-3.1). Self-reported asthmatics had significantly lower mean values for lung function test variables in comparison with non-asthmatics after adjusting for age and height.

Another study examined symptoms, lung-function and serum IgE levels in 98 farmers with 98 non-farmers in the United Arab Emirates (Bener, Lestringant et al. 1999). The two groups were equivalent in age, sex and region of origin. Use of a range of pesticides by farmers was high (60.2%). Farmers had a significantly higher self reported prevalence of chronic dermo-respiratory symptoms including asthma ($p < 0.008$), and contact dermatitis ($p < 0.02$). Spirometry results were also significantly reduced in farmers.

There is also evidence that metam sodium, a herbicide widely used in the USA can act as a contact sensitiser in humans, inducing allergic dermatitis. It also may exacerbate or induce respiratory allergy (asthma) (Pruett, Myers et al. 2001). One retrospective clinical case series of 197 subjects from communities situated within one-half mile of an environmental spill of metam sodium reported the occurrence of persistent respiratory disorders, including irritant-induced asthma (Cone, Wugofski et al. 1994). 20 cases of persistent irritant-induced asthma and 10 cases of persistent exacerbation of asthma were identified from this sample.

Captafol has also been reported in a case study as a cause of work-related asthma after several years of exposure (Royce, Wald et al. 1993).

Several studies have looked at the effect of pesticides on the immune system. Altered immune function may offer a possible mechanism that might contribute to the development of asthma. In one small study, twelve individuals were exposed to chlorpyrifos and followed-up for 1-4.5 years to determine changes in the peripheral immune system (Thrasher, Madison et al. 1993). The subjects were found to have higher rates of atopy and autoimmunity when compared with two control groups. Notably, chlorpyrifos was one of the main tickicides used during the period when significantly raised mortality from asthma was identified. Another recent study in Inuit infants suggested DDT exposure in subjects was related to the incidence of otitis media, although no changes in immunological parameters were detected (Dewailly, Ayotte et al. 2000).

Asthma is also a common symptom in individuals identified with multiple chemical sensitivity (Baldwin, Bell et al. 1997; Ziem and J 1997). A "reactive airways dysfunction syndrome" has recently been coined to describe a condition that exhibits features of both asthma and chemical sensitivity(Ross 1997). There is substantial overlap between chemical sensitivity and chronic fatigue syndrome, which may even be different expressions of the same disorder (Ziem and J 1997). The survey of surviving subjects identified a significantly higher self reported prevalence of chronic fatigue syndrome. There was also a significant association in the survey between subjects reporting chronic fatigue syndrome and asthma, after adjusting for age and smoking.

This study provides reasonably strong evidence supporting a possible causative association between working as a Dipper and asthma. These include the consistency of the findings in comparisons with both the general community and controls (thus controlling for some extent for confounding by smoking), and the finding of increased prevalence of asthma and atopy in the cross-sectional study of surviving cohort members. Existing research suggesting an

association between one of the main chemicals used during the relevant exposure period and atopy lends a physiological plausibility to this argument.

However, insecticide exposure is not the only possible explanation for this association. Cattle, themselves, are recognised as a cause of occupational asthma (Dewdney 1984), and altered immune responses can be demonstrated in symptomatic subjects exposed to cow dander and urine (Ylonen, Mantyjarvi et al. 1992). While a recent survey of Danish youth failed to find an association between occupational farming exposure and either lung symptoms or lung function (Omland, Sigsgaard et al. 1999), studies of dairy farmers working with cattle in confined spaces have found minor changes in lung function (Heller RF, Hayward et al. 1986; Rautalahti, Terho et al. 1987). A study of self reported symptoms in 1542 Swiss farmers (Danuser, Weber et al. 2001) found a non significant increase in asthma in those working with cattle compared to other farmers adjusted for age and smoking status (OR 1.88; 95% CI 0.69-5.17), although asthma in the total study group was less than in the general Swiss population (OR 0.64; 95% CI 0.31-1.34).

It is therefore possible that the increased mortality from asthma and the increase in self reported atopic symptoms among Dippers reflect, at least in part, an immune response to cattle themselves. This possibility would be supported if mortality from asthma was consistently elevated across study periods. While, asthma mortality is, indeed, increased in all chemical periods both when compared to the Australian population and controls, the greatest increase is during the period of modern chemical use. These findings would be consistent with either hypothesis.

Another possible explanation for the findings in this study is they are the result of several factors acting together. If individuals working with cattle face an ongoing immune challenge, perhaps the degree of their response may be modified by their exposure to pesticides.

5.2.8 **Diabetes**

When compared to the Australian population, Dippers as a group working in the modern chemical period had an increase in mortality from diabetes of borderline statistical significance (SMR 3.00; 95% CI 0.97-7.00). This association was statistically significant when exposure lag models other than the 10 year default used in analysis were applied. For Dippers as a group working in the early period of modern chemical use (1963-1976) this increase was also significant. There was also significantly increased mortality for Dippers as a group over the total study period in the less than 5 years exposure group. This same group had a statistically significant increase in mortality when compared to controls. There were also large increases in mortality when Dippers were compared to controls over different chemical periods, particularly the modern era, although none of these were significant.

The survey of surviving cohort members identified 44 subjects who reported suffering from diabetes. Of these 23 were controls and 21 Dippers. Analysis identified only a slight increase in diabetes prevalence when Dippers were compared to controls after adjusting for age. However, when disease prevalence was compared with chemical exposures, diabetes was significantly associated with subjects reporting occupational herbicide use. This association was surprising as it was atypical of disease patterns either for subjects reporting herbicide use, or for those reporting the use of other pesticides.

A number of factors suggest the increased death rates from diabetes identified in the analysis were real. Firstly, the association is relatively large and seems to relate to a specific chemical period (post 1963), suggesting a specific exposure during this time exerted an effect. Mortality is not raised for the control group, suggesting the outcome was not influenced by an underlying lifestyle difference. There was, however, a slight increase in Dippers not yet past the 10 year exposure lag, although this was limited to a single case over the entire study period. A true association is also supported by the finding in the study survey of a higher prevalence of diabetes among subjects reporting herbicide use.

On the other hand, if herbicide use was the exposure responsible for the identified increase in mortality, why was there no concomitant increase among controls who reported occupational

herbicide use almost as frequently as Dippers in the study survey. One explanation might be that herbicide use only became widespread among council workers more recently than among Dippers. Another might be variation in the type of herbicide used by each organisation over different periods.

NSW Agriculture reports that herbicide use among staff of the cattle dipping program was infrequent and a minor part of their duties. However, exposure in the modern chemical period extended back to 1963, so past practices may have been lost to corporate memory. Self reported diabetes was scattered among subjects drawn from all councils participating in the study so the prevalence also does not appear to relate to differing herbicide use between employers. When local governments were asked to describe their past herbicide use, no clear pattern emerged, although glyphosate has become the most widely used chemical in recent years. Before 1980, a wide range of chemicals were used including 2,4 D and 2,4,5 T, substances present in Agent Orange used in the Vietnam war during operation Ranch Hand.

There is some recent evidence from other studies that supports a possible association between herbicide exposure and diabetes. A study of 989 veterans of Operation Ranch Hand examined the relationship between serum TCDD levels and glucose abnormalities including diabetes (Henriksen, Ketchum et al. 1997). Diabetes prevalence increased with increasing exposure to TCDD, a contaminant of the herbicide Agent Orange. In another study, TCDD levels in subjects living near a contaminated site were associated with plasma insulin levels.

Little other research has been done on diabetes and pesticides, although a 1967 study of 59 highly exposed workers at the Montrose chemical factory in the US found high DDT levels in fat and an 8.6% prevalence of diabetes (Laws, Curley et al. 1967). A study of 3579 United States workers involved in the production of DDT found increased mortality from diabetes, but not in those thought to be exposed to DDT (Wong, Brocker et al. 1984), and an early cohort study of 2,620 pesticide exposed workers suggested a higher prevalence of diabetes in subjects with high DDT levels, but this was flawed by a low response rate and reporting bias (Morgan, Lin et al. 1980). Another study calculated Proportionate Mortality Ratios from 748 deaths

among corn wet-milling workers and found increased mortality from diabetes and a threefold excess of pancreatic cancer deaths among blacks (Thomas, Krekel et al. 1985).

Several case studies have been reported of diabetes induced by pesticide poisoning (Takahashi, Toya et al. 2000), and one study of 23 subjects admitted to an Indian intensive care unit with carbamate or organophosphate poisoning found 69% of subjects demonstrated transient glycosuria (Shobha and Prakash 2000).

There is also some evidence to suggest that diabetes may be a risk factor for pancreatic cancer, although this is conflicting (Calle, Murphy et al. 1998). This raises the intriguing possibility that the increases in mortality from diabetes and pancreatic cancer identified in this study are related. Diabetes is also a risk factor for circulatory disease. This thesis has generally ascribed high rates of circulatory disease among Dippers and controls to an increased prevalence of smoking compared to the Australian population. An alternative explanation might be higher rates of diabetes in both subcohorts, themselves a result of pesticide exposure.

While the findings of our own study are difficult to interpret, they present reasonably convincing evidence of an increase in diabetes prevalence and mortality as a result of pesticide exposure. Whether this increase relates to a particular chemical or class of chemicals is unclear. It is also possible that the findings may reflect the result of multiple chemical exposures. Diabetes warrants further investigation as an outcome in studies exploring the impact of pesticide exposure.

5.2.9 Survey of surviving subjects

As described above, a number of sources of possible bias in this cross-sectional study limit the weight than be put on its findings. Nevertheless, prevalence of a number of outcomes was significantly raised among Dippers, generating several research questions that may fruitfully be pursued by other studies.

Part of the survey of surviving cohort members consisted of a questionnaire designed to identify disorders of the central nervous system. This questionnaire was originally developed and validated in solvent exposed workers by Hogstedt (Hogstedt, Andersson et al. 1984). The questionnaire does not contain questions concerning differential aetiologies or diagnoses, but is designed to elicit information regarding symptoms of the early effects of neurotoxic exposures in working populations in a standardised manner. Validation studies have been undertaken to examine its test-retest reliability, sensitivity in discriminating exposed and non-exposed populations, and its ability to detect other outcome measures (Safety 2001), although some have questioned the predictive validity of the questionnaire (Smargiassi, Bergamaschi et al. 1998). As with other components of the survey, responses are subject to reporting bias.

The relationship of subject group with the logarithm of the total score + 1 was explored using analysis of variance techniques. Responding Dippers had a significantly higher log score +1 than controls, after adjusting for age indicating worse neuropsychological status.

There was little evidence from the mortality database to support these findings. While there was a non significant increase in mortality from brain cancer (described above), this related to only 3 cases since 1962. Parkinson's disease was also uncommon and only occurred in subjects over 70 years of age. When mortality from all disorders of the central nervous system was compared between the subcohorts, there was also no significant increase in deaths. Nor was there an increase in deaths from mental disorders.

While there was little other evidence from the study to support or refute the association between the exposed group and a worse neuropsychological score, there is a large body of other research indicating that high pesticide exposure can affect both the central and peripheral nervous systems. Organophosphates, in particular are known to be associated with several sub acute, delayed and chronic neurological, neurobehavioural and psychiatric syndromes. These include a well defined "intermediate" syndrome, organophosphate induced delayed neuropathy (OPIDN, mediated through inhibition of neuropathy target esterase) and a number of chronic neurological and psychiatric disorders (Abou-Donia 1981). A number of epidemiological studies have suggested an association between chronic pesticide exposure, in

particular organophosphates, and adverse neuropsychological outcomes, although this is not universal (Daniell, Barnhart et al. 1992; Stephens, Spurgeon et al. 1995; Stokes, Stark et al. 1995; Beach, Spurgeon et al. 1996; Amr, Halim et al. 1997; Fiedler, Kipen et al. 1997). Almost all studies have been small and involved clinical assessment.

The worse neuropsychological score recorded by exposed subjects in response to the survey questionnaire is consistent with the contention that pesticide exposure can adversely affect the central nervous system. However, as described above, the survey itself is vulnerable to a number of different forms of bias, in particular reporting bias, and there is also little support for the findings from mortality patterns identified in the main analysis. For these reasons the results cannot be viewed as strong evidence of adverse neuropsychological impacts from subject's occupational pesticide exposure.

The key other outcomes that were found to be increased amongst subjects of the exposed subcohort were asthma/ eczema, chronic illness and arboviral disease. Asthma and other atopic conditions are discussed above.

Arboviral disease is common in the study area, with over 100 infections of Ross River Virus and Barmah Forest Virus generally being notified to the NSW Health Department each year (Notifiable Diseases Database system, Health Protection Branch, NSW Health). As outdoor workers potentially exposed to mosquitoes, it is not surprising that Dippers would have high infection rates from these diseases. However, the control group is also composed of outdoor workers, and it is somewhat surprising that there would be a significant difference in infection rates between the two groups. A possible explanation may be the location of Dips themselves, which were generally built beside rivers or streams for access to water. This environment would quite likely be more mosquito prone than the roads and other more open environments that more typically were the occupational setting for control subjects. On the other hand, this result may simply reflect reporting bias between the two groups.

A more complex issue is the significantly higher reported prevalence of "recurring ill health" and, to a lesser extent, "chronic fatigue syndrome" among exposed subjects. Without

corroborating evidence from other sources, it is difficult to assess whether this is the result of reporting bias or reflects a genuine difference in health status between the groups. Some support for these findings comes from studies into multiple chemical sensitivity, but this field of research is poorly developed and lacks even a clear definition of the clinical entity (Baldwin, Bell et al. 1997). There appears to be a substantial overlap between chemical sensitivity and chronic fatigue syndrome, which may even be different expressions of the same disorder (Ziem and J 1997). While this study suggests that past occupational exposure to chemicals may have an adverse impact on general ill-health, and may be associated with chronic fatigue syndrome, teasing out the influence of bias and/or exposure for these findings is not possible.

5.3 STUDY FINDINGS - EXPOSURES

An interesting feature of this study is the capacity to examine changing mortality patterns over time, in particular over periods of different chemical use. These have been used throughout the analysis. This categorisation by chemical period has a number of limitations that need to be borne in mind when considering results.

Firstly, because most subjects worked over a period of many years, few worked only in one period of chemical use. Only 4 Dippers worked only during the period of arsenic use, while120 Dippers were identified as working exclusively during the period of DDT use. Since the changeover of chemicals in dips was staged, even these categories are somewhat blurred, and it is known that many dips contained arsenic until well into the DDT era. Especially during the years immediately following the introduction of DDT, many subjects may have therefore not been working with DDT at all and any analysis of associations between this category of subjects and an outcome will be biased to the null.

Similarly, during the modern chemical era, no effort has been made to distinguish between particular types of chemicals. Most workers during this period are likely to have been exposed to a range of organophosphates, carbamates and other chemicals. This lessens the power of the

study to identify an association between a specific chemical and a specific outcome. On the other hand, to the extent it allows for the possibility of interactions between chemicals it may identify associations that may not have been apparent if subjects had only faced one chemical exposure.

Similarly, while it is likely exposed subjects faced continued high exposures to the chemical of the day, it is probable that at some times, for example when chemicals were changed over, they faced even higher exposures. Thus, there is the opportunity for considerable variations in exposure within period categories, although almost all Dippers would have faced regular high pesticide exposures of some sort.

Finally, the numbers involved in analysis of both the arsenic and DDT periods are small with consequent impacts on study power. On the other hand, these small numbers mean that the occurrence of relatively small number of events may suggest large relative increases in mortality that are really the result of chance.

When the impact of smoking is examined across the different chemical periods, it appears to be fairly consistent both for exposed subjects and controls. Circulatory disease, respiratory disease and lung cancer all remain relatively stable, perhaps with a trend to increasing mortality in later years. The highest all cause mortality for both groups occurs in the modern chemical period, perhaps reflecting this trend.

5.3.1 Arsenic

Arsenic is known to be associated with increased mortality from skin cancer, a range of internal cancers and circulatory disease (Tseng, Chu et al. 1968; Chen, Chuang et al. 1986; Stohrer 1991). Few of these are apparent in this study, although deaths from circulatory disease are significantly increased in the group most exposed to arsenic when compared to controls (SIR 1.82; 95% CI 1.27-2.60). However, the overall mortality from circulatory disease in arsenic exposed Dippers compared to controls is only marginally increased, and mortality from circulatory disease of all arsenic exposed Dippers is reduced when compared to the general

Australian population. This finding is therefore compatible with the results of other studies, but not entirely convincing.

One difference between this study and others examining the impact of arsenic exposure on health is the route of exposure. Studies looking at skin cancer and internal malignancies have generally focused on subjects exposed to arsenic in drinking water, while subjects with high mortality from lung cancer have generally (though not exclusively) been exposed by inhalation. While Dippers would have faced some exposure by these pathways, the more important exposure route for these subjects is dermal. The impact of these differences is uncertain.

5.3.2 DDT

DDT has been the subject of a large number of studies, which are often made easier by its persistent nature and accessibility for biological monitoring. However, many of these studies have been weakened by methodological problems and their results are inconsistent. Perhaps the most intensively studied outcome is breast cancer, which has little direct relevance to this all male cohort. Other associations that have been identified include diabetes, pancreas cancer, lung cancer, leukaemia, non-Hodgkin's lymphoma, and endocrine disruption. While the results of this study are not inconsistent with these findings, the only outcome with significantly increased mortality in DDT exposed subjects compared to controls (thus partly controlling for smoking) was pancreatic cancer. This is discussed above.

5.3.3 Modern Chemicals

The period since 1963 has seen a wide range of insecticides used by the cattle dipping program. Most are still in use for a range of agricultural purposes. The range of possible associations identified in the literature for this diverse group is vast.

While more cohort members worked during this era than in the two other exposure periods, the opportunity for follow-up was less. The ability for the study to identify true associations during this period may therefore be limited, particularly if the time necessary for disease development is large. This is exacerbated by the variety of potential exposures that meant an

individual Dipper working during this period might only have faced minimal exposure to some of the chemicals in use.

Small numbers of outcomes in both exposed and control subjects also means SMRs and, particularly, SIRs were more volatile in this period, with a number of large, but non-significant, increases.

Mortality from several diseases was increased for this period. When compared to the Australian population, deaths from smoking related disease were slightly increased, though the increase in controls was slightly greater. There was a large significant increase in mortality from asthma, an increase in mortality from diabetes of borderline significance and a non-significant increase in emphysema. All other SMRs for exposed subjects were less than 2. When compared with the control population, asthma, diabetes and lymphocytic leukaemia all had large but non significant increases in mortality. Total cancers were increased significantly for Dippers working over 15 years, as was myeloid leukaemia. However, total mortality from both types of leukaemia was small and the implications of these findings were uncertain.

There was, however, some evidence from the survey of surviving cohort members to support the identified associations of asthma and diabetes with exposure to chemicals during this period.

6 SUMMARY

At the simplest level, this study examines whether the mortality of staff working in the NSW Tick Control Program was greater than that experienced in the general community. There is clear evidence that this is the case, with a significantly increased mortality for all staff working during the study period.

However, the main intent of the study was to identify whether it was these subjects' occupational exposure to pesticides that influenced their pattern of mortality, in order to understand the implications for other workers and the broader community. The study tests the hypothesis "That repeated high exposure to insecticides in an historical cohort of agricultural workers increased their rates of death and morbidity compared to a control cohort and the Australian population"

As outlined in the literature review, a major problem with epidemiological research into the health impact of pesticides is exposure assessment. This and other methodological difficulties have resulted in a limited and disjointed current body of evidence on whether or not non-acute pesticide exposure results in adverse health impacts.

This study shares some of these methodological problems. Exposure was defined using occupational categorisation, and exposure dose by duration of employment. This approach is most effective if exposure is constant over time. Both anecdotal evidence and limited biological monitoring suggest exposure in cattle dipping staff was consistently high, however a range of insecticides were used during the study period and different subjects were exposed to different chemicals at different times. While this allows for analysis of the impact of specific chemicals in different periods, it also tends to mask associations that are the result of exposure to a single chemical, since the experience of subjects exposed to that chemical are pooled with those of non exposed subjects.

The occupational categorisation used in this study also does not distinguish between insecticide exposure and the possible influence of a range of other possible exposures faced by cattle dippers including biological exposure to animals and microbes.

However, the unusual design of this study overcame some of the other problems evident in the scientific literature. Including a control group allowed some assessment of the degree of confounding by smoking and other lifestyle factors on the cohort outcomes. While these two sub cohorts were not drawn from the same parent population, a range of evidence suggests they shared similar but not identical lifestyles. A small amount of biological monitoring supported assumptions about pesticide exposures in these two groups. The healthy worker effect also appears to have been largely overcome by the study's long follow-up period.

While overall mortality was increased amongst exposed subjects, this was largely due to significant increases in mortality from smoking related diseases such as circulatory disease, respiratory disease and lung cancer. These same patterns of disease were generally shared by the control group of other outdoor staff from the same area, and by exposed staff who had not yet worked for 10 years suggesting they were independent of insecticide exposure.

However, mortality from several other causes was also increased among Dipping staff. Those working during the period of DDT use had increased mortality from pancreatic cancer, and for those working less than 3 years, this was statistically significant when compared to both the control group and the Australian population. This supports limited other evidence in the scientific literature for a relationship between DDT and pancreatic cancer.

Dippers as a group working at any time during the study period were more likely to die from diabetes, and for those working less than five years, this was statistically significant. Mortality from diabetes was significantly increased for Dippers working between 1963 and 1976. Mortality from diabetes was also increased when Dippers were compared to the control cohort and, for those working less than 5 years, this was statistically significant. There was also some support for this finding in a survey of surviving cohort members. Subjects reporting occupational herbicide use had a significantly increased prevalence of diabetes. Other research has also identified a possible link between diabetes and the dioxin-contaminated herbicide Agent Orange.

Similarly, evidence was found for both increased mortality from asthma and increased prevalence among surviving members of the exposed sub cohort. While it is possible these associations might be confounded by the influence of smoking, mortality from asthma was also significantly increased in Dippers when they were compared to the control group, suggesting the influence of smoking was limited. The association was not evenly distributed over the study period, suggesting it was also not the result of other, non-insecticide, occupational exposures such as cattle.

Mortality from leukaemia was elevated for Dippers working during the era of modern chemical use and this increase was significant when subjects in the highest exposure category were compared to the control group. Both lymphatic and myeloid leukaemia were elevated for Dippers working during this period when compared to the control group, and the increase in mortality for myeloid leukaemia was significant. These results are somewhat ambiguous, but they are consistent with the findings of a number of other studies.

The study also identified non significant increases in mortality from a number of other conditions previously suggested as possibly related to pesticide exposure. These include Non Hodgkin's Lymphoma, brain cancer and prostate cancer. Failure to identify these increases as significant may reflect the methodological limitations and power of the study, and the findings do not conflict with the possibility these may in fact be true associations.

While the survey of surviving cohort members identified possible associations of several self reported outcomes with membership of the exposed subcohort, methodological flaws limit the weight that can be put on this evidence. Possible associations identified in the survey included neuropsychological dysfunction, chronic fatigue syndrome and atopic conditions.

The response to the study hypothesis therefore has to be in the affirmative. While the evidence generated by this study is not definitive, it appears that, after accounting for the influence of other known confounders, mortality from several conditions was increased in this cohort of insecticide exposed staff.

The findings have implications for other workers, and, to a lesser extent the general community. Pesticides are very widely used, and there is limited evidence available on what, if anything, constitutes safe exposure. The results of this study support limited existing evidence that high exposures to DDT are related to pancreatic cancer and identify two new areas that are worthy of investigation, diabetes and asthma. They also lend some weight to the existing knowledge of that pesticides may impair neuropsychological function and be in some way related to chronic fatigue syndrome, although this needs to be tempered by the methodological limitations of this aspect of the study.

Recommendations:

- That the possible associations identified in this study are the subject of further investigation.
- That researchers strive to improve the current limited body of epidemiological research in this field.
- That relevant authorities continue to develop strategies to minimise exposure to pesticides in occupational settings and the broader environment.

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