AN INVESTIGATION OF THE RELATIONSHIP BETWEEN OCCUPATION AND MALE INFERTILITY

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"A good epidemiologist is cautious and critical, not paralysed"

Geoffrey Rose, Oct 1988.

This thesis is dedicated to my parents

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ABBREVIATIONS AND TERMS

The following is a list of abbreviations, terms and their definitions which were used in this thesis:

Terms:

Azoospermia	The absence of sperm in the ejaculate
Aspermia	No ejaculate
High sperm deformity	This was the term used in this thesis to define the presence of a high proportion of abnormally formed sperm and was defined as 70% or greater abnormal forms *ie* fewer than 30% sperm with normal morphology [WHO, 1987] The technical term for this is teratozoospermia
Low sperm motility	This was the term used in this thesis to define the presence of a high percentage of sperm with poor motility and was defined as 50% of less motile sperm [WHO, 1987] The technical term for this is asthenozoospermia
Oligozoospermia	Low sperm concentration Defined by the WHO as 20 million sperm per ml or less [WHO, 1987] This is often referred to as oligospermia
Spermatozoa	Referred to in short as sperm

Abbreviations:

ART	Assisted reproductive technologies
CASA	Computer-assisted semen analysis
CI	Confidence interval
CNS	Central nervous system
DBCP	1,2-dibromo-3-choloropropane
EGEE	Ethylene glycol monoethyl ether
EGME	Ethylene glycol monemethyl ether
ESHRE	European Society for Human Reproduction and Embryology

GIFT	Gamete Intrafallopian Transfer (one of the ARTs)
GHS	General Household Survey
IVF	*In Vitro* Fertilization
KDGH	Kettering District General Hospital
LGH	Leicester General Hospital
LRI	Leicester Royal Infirmary
nec	Not elsewhere classified
NHS	National Health Service
OPCS	Office of Population Censuses and Surveys (now know as the ONS)
OR	Odds ratio
OTA	United States Office of Technology Assessment
OTM	Oxford Textbook of Medicine
PNMS	The Leicestershire Perinatal Mortality Survey which is a case control study
SEG	Socio-economic group
SMR	Standardised mortality ratio
UK	United Kingdom
VDU	Computer Visual Display Unit
WHO	World Health Organisation

ABSTRACT

Aims To test the hypothesis that leather work is associated with male infertility, mediated through the development of oligozoospermia (low sperm concentration). The basis of any association was thought, *a priori*, to be with exposure to the solvents used in leatherwork.

Methods An unmatched case control study was designed. Interviewer administered questionnaires collected occupational details and other information from 1906 men (88.5% response) who presented with their partners as new referrals for the investigation of infertility in Leicestershire and at Kettering hospital between November 1988 and September 1992. Two sets of comparisons were made. First the Leicestershire infertility presenters were compared as cases to 1013 fathers of control babies from the Leicestershire perinatal mortality survey. Second, a 'within infertility' analysis, restricted to the presenters with infertility, compared the characteristics of those men with oligozoospermia (cases) to those without (controls).

Results The unadjusted odds ratio (OR) for presenting for the investigation of infertility associated with leatherwork was 1.10 (95%CI 0.46, 2.63). The adjusted OR for the development of oligozoospermia associated with leatherwork was 1.20 (95%CI 0.43, 3.35) and there was only a 17% chance that the true relative risk was 2.0 or greater. Adjusted results indicated that leatherwork was associated with only an estimated 6.0% reduction (95%CI -44%, +55%) in sperm concentration. The adjusted OR for oligozoospermia, low motility and high sperm deformity associated with solvent work were all 1.31 or below and were not statistically significant.

Conclusions There was little evidence to support the hypothesis that leatherwork is a risk factor for oligozoospermia. Overall the findings provide reassurance for the leather industry which uses leather in manufacturing. Further investigation into a possible relationship with high sperm deformity is recommended. The results also suggest that exposure to work with solvents is not a risk factor for oligozoospermia, although less reassurance can be taken from these findings as exposure misclassification is likely to have had an effect.

BACKGROUND

1.1 INTRODUCTION

The depth of anguish and despair felt by couples who are unable to conceive is unimaginable to those not similarly affected. Those who are infertile experience the full range of emotions which accompany the biological drive to procreate.

The family plays a fundamental and central role in our society and couples facing involuntary childlessness often feel peripheral to this central social institution [Houghton, 1984]. This leads to a sense of isolation, alienation, feelings of 'thwarted love', denial, anger, grief and a concern about genetic death since it is our children who provide continuity with the past and future [Houghton, 1984; Menning, 1980]. Whilst the feelings associated with involuntary childlessness may reach some resolution they are likely to be life-long and indeed may never abate [K Miller - personal communication].

Infertility is a biological condition which leads to the social condition of involuntary childlessness. Of newly married couples 95% want and expect to have children of their own at some stage [Glick, 1977]. In fact this is such an "expected reality" in our society that Matthews and Matthews [1986] have described the stages of family life as being a dichotomy between the "family of orientation" (early, usually contracepting, marriage) and the "family of procreation". By its nature involuntary childlessness must involve a major reconstruction of the reality experienced by infertile couples [Matthews & Matthews, 1986]. It is in this context that infertility is experienced as an acutely private sorrow whilst, at the same time, the investigation of infertility invades the most private aspects of a couple's life and can be accompanied by the, often vigorously expressed, pronatalistic expectations of

family, friends and even acquaintances.

Until quite recently, infertility has largely been regarded as a 'female problem'. This is reflected in the location of most infertility clinics in the gynaecological setting. Indeed, the male contribution to reproduction has been described as one sperm and a box of cigars [Sever, 1995]. This emphasis on the female origins of fertility and infertility has been reinforced by recent developments in the assisted reproductive technologies (ART) namely *In Vitro* Fertilisation (IVF), Gamete Intrafallopian Transfer (GIFT) and related procedures. These palliative procedures have side-lined the need for detailed investigations and treatment of the pathophysiology of male factor infertility and the 'treatment' itself has a female focus [Jequier, 1993; Cummins & Jequier, 1994]. Such developments also risk leading to a decline in the focus on aetiological research. Nevertheless, despite the historical and continuing focus on the female aspects of infertility, it is clear that male infertility is of great significance and the aetiology of male infertility should not be ignored.

The work presented in this thesis sought to investigate the relationship between a particular aspect of occupational exposure, namely leatherwork, and the risk of male infertility. The definition of infertility, estimates of occurrence, the pathophysiology of male infertility and the role of occupational exposures in the aetiology of infertility will be discussed here as a background to the study presented. Quite deliberately, given the nature of the study conducted, parts of this discussion will centre on male infertility to the exclusion of female aspects.

1.2 DEFINITION OF INFERTILITY

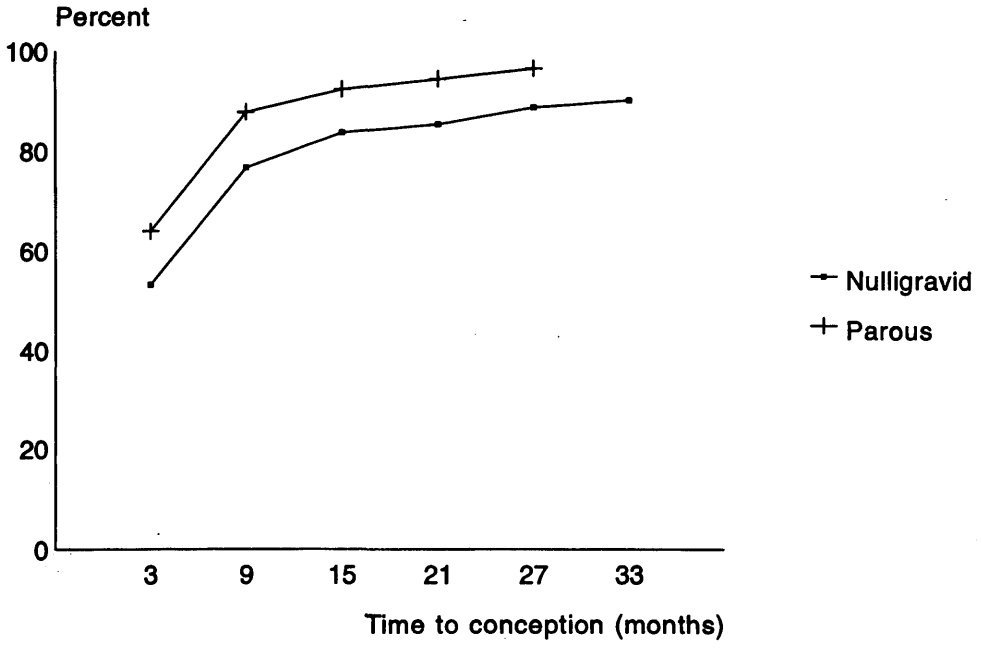
In common with many diseases, such as diabetes and hypertension, the definition of infertility largely depends on the 'choice' of a cut-off on the spectrum of normality to abnormality, that is fertility to infertility. Only in the extremes of abnormality such as sterility (*ie* no possibility of natural conception) is the definition clear. However, even in this extreme, since sterility can occur without obvious stigmata, a period of attempted conception may pass before the diagnosis is made and the definition fulfilled.

1.2.1 Natural levels of fertility and the relationship to infertility

The definition of infertility largely depends on being the converse of the definition of 'normal' fertility. However, with the widespread use of contraception in modern industrialised societies the concept of a 'level of natural fertility' is now largely a theoretical one [Leridon, 1977]. Fertility data from modern non-contracepting populations are available, however, the general applicability of data from such groups as the Hutterites or Amish in the USA is questionable. Religious, cultural and nutritional factors all have a role to play in fertility and the religious, cultural and dietary practices of these selected societies are generally at variance with those of the wider population. Data from the Oxford Family Planning Association Contraceptive Study provides information of probably more relevance to modern European industrial populations [Vessey *et al*, 1978]. Although, extrapolation of the data to the general population is to some extent limited by the fact that there may have been some selection bias towards certain sections of the population in relation to the contraceptive method chosen. Furthermore, only married, white, British subjects were included in this study and women with a history of ovarian or uterine tumours, pelvic inflammatory disease, amenorrhoea or oligomenorrhoea were excluded as were nulliparous women with a history of miscarriage or termination of pregnancy. In terms

of natural fertility, probably the most useful data relate to the proportion of women who remained undelivered over time amongst those women who had discontinued the use of the diaphragm and had never used the oral contraceptive pill. The time to conception of women who had discontinued contraception can be inferred from the published data assuming that the average duration of pregnancy was nine months; the inferred results are shown in figure 1.2.1.

Figure 1.2.1: The time to conception for women from the Oxford Family Planning Association Study who had discontinued the use of the diaphragm [From Vessey *et al*, 1978]



As can be seen from the figure approximately 80% of nulligravida women had conceived 12 months after discontinuing contraception and over 85% had conceived by 24 months. For parous women approximately 90% had conceived by 12 months and about 95% had conceived by two years. It should be noted however, that these figures underestimate the

proportion of women who would have actually conceived since women had to have delivered in order to be included in the published data set. Thus women who had a spontaneous or induced abortion would not have been included.

The Oxford data, as illustrated, provide a picture of 'natural fertility'. It is against such a background that current definitions of infertility can be derived and reflected upon.

1.2.2 Definition of terms

There are a number of terms and definitions used to describe the failure to conceive a desired pregnancy. The condition is variously described as subfertility, subfecundity, infertility and sterility. In demographic terms fecundity refers to the ability to produce live offspring and is difficult to measure in practice as it refers to the theoretical ability to conceive and carry a fetus to term with a resultant live birth [Last, 1988]. In contrast fertility defines the actual production of live offspring [Last, 1988]. As a demographic measure fertility excludes stillbirths, fetal deaths and abortion (both spontaneous and induced). Thus, the converse of fertility, that is infertility, using this definition, is logically defined as the inability to produce live offspring. However, in clinical and aetiological terms this demographically based definition of infertility makes little sense since the causes and management of an inability to conceive have little in common with the causes and management of spontaneous abortion, fetal death and stillbirth [Belsen, 1984]. In current clinical practice infertility is generally, although not universally, defined as the "failure to conceive a clinically recognised pregnancy by a couple having regular sexual intercourse for at least a year without the use of contraception" [Hammond, 1994]. However, as illustrated below, this clinical definition has not been universally used in studies to estimate the population occurrence of the condition. Furthermore, the clearly defined demographic

terms fecundity and fertility have been highjacked for use by other disciplines and different definitions have been applied to these terms, as illustrated below.

In 1975 the World Health Organisation defined infertility as "unable to conceive despite cohabitation and exposure to pregnancy for a period of two years." [WHO, 1975].

In 1985 Mosher and Aral presented an analysis of data from 1965, 1973 and 1976. In this analysis to be classified as infertile "a couple must not have used contraception for 12 months or more of continuous marriage, and they must not have conceived in that time or been surgically sterilized" [Mosher & Aral, 1985]. In 1991 Mosher and Pratt used the term infertility to refer to "12 or more months of intercourse without contraception and without becoming pregnant" [Mosher & Pratt, 1991]. They also used the term "impaired fecundity" which was defined by the answers at interview to a series of questions as "it is difficult or impossible to conceive a baby or difficult or dangerous to carry it to term."

Infertility was defined by Hull *et al* [1985] as "failure to achieve any pregnancy (including miscarriage) for at least 12 months"; Thonneau *et al* [1991] used a similar definition. Whereas in 1990, Thonneau and Spira defined infertility as "the involuntary absence of conception after a period of exposure (generally 1 year)..." [Thonneau & Spira, 1990]. Page [1989] used a more explicit and extended version of this definition as having "engaged in sexual intercourse without conception for more than one year". Schmidt *et al* [1995] and Buckett & Bentick [1997] used essentially the same definition as Page, although again the wording was slightly different. Webb and Holman [1992] went on to extend the definition further and to exclude couples with surgical sterility. They defined infertility as an inability to conceive "after one year of unsuccessful efforts to become

pregnant, marked by a continuous relationship with intercourse unprotected by contraception or surgical sterility." Thus, under their definition a couple attending for IVF treatment following vasectomy or female sterilisation would not be defined as infertile. Webb and Holman also introduced the concept of reproductive disability which refers to the perceptions of the couple regarding the existence or not of a fertility or sterility problem. They pointed out the importance of this concept in terms of service provision requirements.

An infertility problem was deemed to exist by Templeton *et al* [1990, 1991] if women "had failed to conceive after trying for more than two years" or if "they had been trying for less than two years but had been referred for investigation by their general practitioner." To overcome the lack of a clearly defined time period Gunnell and Ewings [1994] reported their findings on the basis of a "failure to become pregnant after 12 and after 24 months of regular unprotected intercourse" and Marchbanks *et al* [1989] used a similar approach.

In 1981 Rachootin and Olsen used the term 'reduced fecundity' to describe the failure to achieve a pregnancy after engaging in sexual intercourse without contraception for two or more years [Rachootin & Olsen, 1981]. However, in a 1982 publication in which they reported the analysis of the same data they used the terms subfecundity and sterility [Rachootin & Olsen, 1982]. Subfecundity was defined as a failure to conceive after engaging in sexual activity without contraception for a period of one year or longer. Sterility was defined as the "failure to produce a live birth up to the point of interview after a period of at least one year of engaging in sexual relations without the use of contraception." By this definition the sterility group included couples unable to conceive together with couples capable of conception but who were unable to produce a live birth and must also by

definition have included anyone pregnant at the time of interview.

Greenhall and Vessey [1990] used the term subfertility and defined it as "failure to conceive after 12 months of regular unprotected intercourse or the occurrence of more than two consecutive natural miscarriages or stillbirths." Sundby and Schei [1996] also used the term subfertility, but used the definition of ".... any life time history of waiting time for pregnancy of more than one year regardless of the number of children born later". Sundby and Schei also used the term permanent infertility and defined that as ".... involuntary childlessness at the end of the reproductive age."

In a paper published in 1995 Schmidt and Münster reviewed the definition of infertility in 18 publications which attempted to estimate the population occurrence of infertility [Schmidt & Münster, 1995]. The only occasion where exactly the same definition of infertility was used was when two publications were by the same authors, that is, Templeton *et al* [1990, 1991] when in fact these two papers published findings from the same study.

This short review of definitions may be seen as a historical progression with a recent convergence of most views on at least the time period used in the definition of infertility. However, the two most recently published authoritative views still do not agree as to the time period involved. In 1988 the United States Office of Technology Assessment (OTA) defined infertility as an "inability to conceive after 12 months of intercourse without contraception" [OTA, 1988]. In contrast, as recently as 1996 the European Society for Human Reproduction and Embryology (ESHRE) published the following definitions [ESHRE, 1996]. Fertility was defined on the basis of the distribution of fecundity observed in the "normal" population and was defined as "achieving a pregnancy within 2 years by

regular coital exposure." The terms sterility, subfertility and infertility were dealt with as: "Those couples who do not achieve a pregnancy within 2 years include the sterile members of the population, for whom there is no possibility of natural pregnancy, and the remainder who are subfertile. The term sterile may refer to either the male or the female, whereas the term subfertile refers to the couple." Fecundability was defined as "the probability of achieving a pregnancy within one menstrual cycle." Fecundity was defined as "the ability to achieve a live birth from one cycle's exposure to the risk of pregnancy." [ESHRE, 1996].

In contrast to the lack of consensus about the general definition of infertility, there is general agreement as the subdivision into primary and secondary infertility. In general primary infertility is taken to refer to never having conceived a pregnancy and secondary to the failure to conceive a second or subsequent pregnancy regardless of the outcome of the prior pregnancy(ies) [Schmidt & Münster, 1995]. Primary infecundity is taken by most authors to refer to the failure to deliver a first live birth and secondary infecundity the failure to deliver a second or subsequent live birth [Schmidt & Münster, 1995].

The terms resolved and unresolved infertility were used by Greenhall and Vessey [1990] to make the distinction between a "subfertile episode that is eventually followed by the production of a child and one that is not" respectively.

It is clear from this brief summary that the definition of infertility is problematic. As will be seen in section 1.3 the lack of a clear, agreed nomenclature and defined terms has serious implications for the estimation of the population occurrence of infertility.

1.3 OCCURRENCE OF INFERTILITY

Over the last three decades there has been a marked decline in fertility, as measured by demographic indices, in most industrialised populations [OPCS, 1991; Rachootin & Olsen, 1980]. The intentional limitation of family size is probably responsible for most of that decline and whilst there is some evidence of a natural decline in fertility the interpretation of the evidence regarding an increase in the occurrence of infertility is conflicting [Rachootin & Olsen, 1980; Mosher, 1982; Page, 1988; Sherins, 1995; Joffe, 1996].

Secular trends in twinning, prior to the introduction of the assisted reproductive technologies (IVF, GIFT and related procedures) have provided indirect evidence of a decline in population fecundity in Denmark between 1931 and 1977 [Rachootin & Olsen, 1980]; there is little reason to believe that this a phenomenon unique to the Danes. More recently evidence of an apparent decline in human sperm quality over the past 50 years has emerged [Carlsen *et al*, 1992; Auger *et al*, 1995; Comhaire *et al*, 1995; Irvine *et al*, 1996]. However, the interpretation of these data remains controversial and contradictory results have been published [Bromwich *et al*, 1994; Olsen *et al*, 1995; Bujan *et al*, 1996; Vierula *et al*, 1996; Lipshultz, 1996; Fisch *et al*, 1996; Paulsen *et al*, 1996; Fisch & Goluboff, 1996; Pajarinen *et al*, 1997]. Nevertheless, regardless of the truth, because the human male has an extensive reserve capacity to produce large volumes of sperm, a decline in sperm quality will not automatically translate into a decline in fertility and an increase in infertility [de Kretser, 1996, 1997].

1.3.1 Methodological issues

There are several inherent difficulties in trying to estimate the population occurrence of infertility which are summarised as follows. (1) Unlike most other diseases infertility is a

condition experienced by two people, not just a disease of one person. Furthermore, it is also possible that a particular woman and a particular man will together experience impaired fertility, yet each, with a different partner may not. (2) As discussed in section 1.2, there is no single, clear, agreed nomenclature with which to define fertility problems; different authors have used many different terms, and even when the same term is used a different definition may be applied to it [Schmidt & Münster, 1995]. (3) There is the related problem of defining the appropriate denominator for the calculation of proportions or rates; many authors have used the whole of their sample when in fact some of the women in the sample may never have attempted to conceive [Schmidt & Münster, 1995]. (4) Information on the sexual and contraceptive behaviour of population samples of couples is required which leads to some difficulties in data collection [Greenhall & Vessey, 1990]. In fact it is rare that couples are actually the source of data, most commonly women alone are sampled and information about their relationship(s) is collected. (5) Couples do not necessarily follow the behaviour defined in the standard definitions of infertility in order to 'test' their fertility [Greenhall & Vessey, 1990]. They may use contraception intermittently or inefficiently and may have intercourse with varying degrees of frequency and regularity. (6) There is the problem of deciding when is the appropriate time in the reproductive life of women or couples to attempt to estimate disease occurrence. Collecting information at the end of the reproductive span means that complete information will be collected, however, it will require recall over many years. (7) The outcome of a fertility problem for any couple which does not resolve itself naturally will depend on the availability of treatment services. (8) Finally, the voluntary or involuntary nature and the social context of the childless state needs to be considered.

The prevalence of infertility is described in many standard gynaecological textbooks as 10% of all unions [Greenhall & Vessey, 1990]. Unfortunately this does little to describe the frequency of occurrence of fertility problems in the population as this summary figure includes various subtypes of fertility problems. It also does not define any aspect of the reference time period, that is calendar time, the time in terms of the chronological age of the population involved, nor the time in terms of the duration of trying to conceive.

A true measure of the fertility of a cohort of women or couples and the infertility they experience can only be estimated when their reproductive life is over, that is after 45 or 50 years of age. This population is then ideal for monitoring changes in patterns of fertility and infertility over calendar time. The reproductive life-time cumulative incidence of infertility together with the voluntary or involuntary nature of childlessness can be estimated. However, whilst it is important, such monitoring information is of limited value for current practitioners and service planners. Studies of the occurrence of infertility more commonly use groups of women from a wider age range. The major limitation of this approach is that many women may not have completed, or even begun, their reproductive careers.

Added to the problem of trying to define the appropriate time frame in which to estimate infertility occurrence is the issue of how to refer to that disease occurrence once it has been estimated. In trying to estimate the frequency of occurrence of infertility most authors have sampled a wide age range of women with some still in their reproductive years and some at the end. The women have then been asked to retrospectively report their reproductive history and history of any episodes of prolonged time to conception. Most authors have then referred to the measure of disease occurrence they have estimated as prevalence. Although, Page [1989] and Webb & Holman [1992] have also attempted to

estimate the incidence rate *ie* a measure of the rate of current new cases. In fact what most authors have actually estimated could be referred to as a reproductive life-time period prevalence. Given the disease occurrence estimated by most authors it is only in this way that the term prevalence could ever be used. However, given the duration of time involved (30 years) and the fact that some cases (new and old) of infertility resolve (naturally or by treatment) it is probably more correct to refer to this measure as reproductive life-time cumulative incidence. Life-time cumulative incidence can also be referred to as life-time risk [Clayton & Hills, 1993].

Given the lack of consensus on definitions and terms, which was outlined in section 1.2.2 and to aid comprehension the following definitions of terms will be applied to the data discussed in the following section. As noted in section 1.2.2 demographic definitions of terms have not been used. The term women rather than couple is used which acknowledges the fact that most of the data to be discussed were collected from women about themselves and not necessarily about the couple(s) of which they are or were a member.

1. Primary infertility - will be used to refer to data relating to the failure to conceive a clinically recognised pregnancy following one (or two years) sexual intercourse without contraception; the time period will be specified for each set of data discussed. Surgically induced sterility will be excluded where information about this was provided in the data source.
2. Secondary infertility - will be used to refer to data relating to the failure to conceive a second or subsequent pregnancy. This will include women who have conceived and delivered a child and women who have conceived but never delivered.
3. Primary infecundity - will be used to refer to data relating to the failure to deliver a

desired first live-born child. The women in this group may have experienced either primary or secondary infertility. Any woman for whom this state of affairs continues to the end of her reproductive life will be involuntarily childless.

4. Secondary infecundity - will be used to refer to data relating to the failure to deliver a desired second or subsequent live-born child.

5. Involuntary childlessness - will be used to refer to data relating to the failure to deliver a desired first live-born child.

6. Voluntary childlessness - will be use to refer to data relating to women who choose not to have a child.

7. The term reproductive life-time cumulative incidence will be used as the measure of frequency of occurrence in preference to prevalence (see discussion above) in relation to data which has retrospectively estimated the occurrence of any type of infertility ever having been experienced. In short this is referred to as life-time risk.

1.3.2 A review of studies and results

In 1984 the Warnock Committee commented "We were surprised at how few data there were on the prevalence of infertility ..... where figures were available they were often out of date and of dubious relevance." [Warnock, 1984]. At that stage the available data were largely either from studies in other countries [Rachootin & Olsen, 1981, 1982] or were demographic fertility statistics derived from vital statistics or limited estimates of childlessness from general sources such as the General Household Survey.

The first two studies carried out in the UK following the publication of the Warnock report provided some additional information. However, the information was limited by being derived from hospital attenders in the study carried out by Hull *et al* [1985] and general

practitioner attenders in the review of general practitioner records by Johnson *et al* [1987]. The study by Hull *et al* provided extensive information about the diagnosis and outcome of infertility clinic attenders but was limited in its capacity to provide good population estimates of infertility occurrence by being based solely on hospital attenders and by the limited ability of the investigators to estimate the catchment population from which their referrals came and thus the denominator population for any of their calculations. The first limitation would have led to an under-estimation of the true population occurrence and the second may have led to under or over-estimate depending on the direction of the errors in deriving the size of the denominator. Similarly the information from the study by Johnson *et al* [1987] was limited in its value by being collected from a general practitioner medical notes review. In this study voluntary childlessness was inferred from the absence of a record in the medical notes of a child and an absence of any reference to a consultation with the complaint of infertility.

Hull *et al* estimated the life-time risk of ever attending a hospital for infertility as 16.8% for an undefined age range of couples [Hull *et al*, 1985]. As 59% of the attenders were reported as nulligravid the life-time risk of primary infertility in this population of clinic attenders can be inferred from the data presented as 10.0% and the life-time risk of primary infecundity can be inferred as 11.9%. Johnson *et al* estimated from their notes review that in 1985, 11% of women aged 35yrs and 3.2% of women aged 50yrs were voluntarily childless and 3.3% and 4.5% respectively suffered from involuntary childlessness.

Since the publication of these two health service attender based studies five population based studies carried out in the UK have been reported [Page, 1989; Greenhall & Vessey,

1990; Templeton *et al*, 1990, 1991; Gunnell & Ewings, 1994; Buckett & Bentick, 1997]. The study by Greenhall and Vessey consisted of two parts. The first, which is reviewed here, was population based, whereas the second was based on age matched hospital controls from a case control study of breast cancer. The data from the hospital based part were not reviewed here because of potential biases arising from the nature of the study population. Templeton *et al* published two papers which related to the same study. In the first [Templeton *et al*, 1990] they reported the results from the cohort of women aged 46-50 years and in the second [Templeton *et al*, 1991] they reported the results from both cohorts of women they sampled who were aged 36-40 years and 46-50 years. In the discussion presented here this work will be regarded as one study. The five studies, summarised overleaf in table 1.3.1, ranged in size from 153 women to 2,377. The women sampled ranged in age from 20yrs to 55yrs, however, no two studies included the same age range of women. The response to the studies ranged from 75.7% to 85.7%.

Based on the results from the four studies that used the definition of infertility which included a time period of one year, the life-time risk of ever having experienced infertility of any type at any stage ranged from 17.3% to 28.0% [Page, 1989; Greenhall & Vessey, 1990; Gunnell & Ewings, 1994; Buckett & Bentick, 1997]. The weighted average (weighted directly by sample size) of these results was 23.6% (95%CI 22.5%, 25.1%). Excluding the data from Greenhall and Vessey on the basis that their definition of infertility also included women who had had more than two miscarriages, the result was 24.5% (95%CI 23.0%, 26.0%). Three of the studies defined infertility on the basis of a two year period [Templeton *et al*, 1990, 1991; Gunnell & Ewings, 1994; Buckett & Bentick, 1997]. On this basis the life-time risk of primary or secondary infertility ranged from 12.0% to 14.6% with a weighted average of 13.4% (95%CI 12.5%, 14.4%).

Table 1.3.1: Summary of the five British population based studies which have estimated the occurrence of infertility

Author Year of publication	Respondents Response (%)	Age range Year of study	Risk* of any infertility (%)	Risk* of primary infertility (%)	Risk* of secondary infertility (%)	Risk* of primary infecundity (%)	Risk* of secondary infecundity (%)	Risk* of voluntary childlessness(%)
Infertility defined by a one year cut off:								
Page 1989	153 82%	20 - 44yrs †	28.0%	**	**	**	**	**
Greenhall & Vessey‡ 1990	872 78%	25 - 44yrs †	20.5%	10.7%	16.2%	3.4%	7.7%	**
Gunnell & Ewings 1994	2377 75.7%	36 - 50yrs †	26.4%	16.1%	15.8%	2.2%	**	8.1%
Buckett & Bentick 1997	728 85.0%	45 - 55yrs †	17.3%	10.6%	7.8%	2.3%	1.9%	8.1%
Infertility defined by a two year cut off:								
Templeton *et al* 1990 & 1991	2008 85.7%	36-40 & 46-50yr 1988	14.6%	9.2%	5.9%	2.9%	3.4%	8.1%
Gunnell & Ewings 1994	2377 75.7%	36 - 50yrs †	12.9%	7.4%	6.6%	**	**	(8.1%)
Buckett & Bentick 1997	728 85.0%	45 - 55yrs †	12.0%	**	**	**	**	(8.1%)

* Life-time risk or reproductive life-time cumulative incidence ** Not estimated in this study † Not given
‡ Only data from the population based section of the study by Greenhall & Vessey [1990] are included here

Three of the studies estimated the life-time risk of ever having primary infertility based on the one year definition, these estimates ranged from 10.6% to 16.1% [Greenhall & Vessey, 1990; Gunnell & Ewings, 1994; Buckett & Bentick 1997]. The weighted average was 13.8% (95%CI 12.7% to 15.0%); excluding the data from Greenhall and Vessey, the average was 14.5% (95%CI 13.3%, 15.8%). From the same three studies the estimates of the life-time risk of ever having experienced secondary infertility defined on the one year basis (this includes some women who may have had primary infertility previously) ranged from 7.8% to 16.2% with a weighted average of 14.0% (95%CI 12.9%, 15.2%); excluding Greenhall and Vessey the risk was 13.6% (95%CI 12.4%, 14.9%).

The studies by Templeton *et al* [1990, 1991] and Gunnell & Ewings [1994] estimated the life-time risk of ever having had primary or secondary infertility based on the two year definition of infertility. The risk estimate for primary infertility from Templeton *et al* was 9.2% and Gunnell & Ewings, 7.4%; the combined weighted result was 8.1% (95%CI 7.3%, 9.0%). The estimates for secondary infertility were 5.9% and 6.6% respectively, with a combined risk estimate of 6.2% (95%CI 5.5%, 6.9%).

Four studies reported the life-time risk of primary infecundity [Greenhall & Vessey, 1990; Templeton *et al*, 1990, 1991; Gunnell & Ewings, 1994; Buckett & Bentick, 1997]. These results ranged from 2.2% to 3.4%. The weighted average risk of primary infecundity was 2.6% (95%CI 2.2%, 3.1%). Three studies reported the life-time risk of secondary infecundity [Greenhall & Vessey, 1990; Templeton *et al*, 1990, 1991; Buckett & Bentick, 1997]. These results ranged from 1.9% to 7.7%, with a weighted average risk of 3.8% (95%CI 3.1%, 4.5%). Three studies all estimated that 8.1% of women were voluntarily childless, the 95%CI for this estimate based on all three results was 7.4% to 8.9%

[Templeton *et al*, 1990, 1991; Gunnell & Ewings, 1994; Buckett & Bentick, 1997].

During the 1970s and 1980s there were seven population based studies of infertility carried out in the USA, Denmark, Sweden and Australia [Rachootin & Olsen, 1981, 1982; Poston & Kramer, 1983; Mosher, 1985; Hirsch & Mosher, 1987; Webb & Holman, 1992; Schmidt *et al*, 1995; Högberg *et al*, 1992]. The findings from these studies are summarised overleaf in table 1.3.2. The findings were largely in keeping with the results from the British studies, although, the estimates of life-time risk of any episode of infertility tended to be lower in the overseas studies than in the British. In addition, two estimates of voluntary childlessness published by Ponston & Kramer were about a quarter of any other British or overseas estimates; it is not clear why this should be so.

Four further overseas studies were also identified [Rantala & Koskimies, 1986; Marchbanks *et al*, 1989; Ghazia *et al*, 1991; Sundby & Schei, 1996]. However, these were either studies carried out for a different purpose and collected information which incidentally allowed infertility estimates to be made [Rantala & Koskimies, 1986; Marchbanks *et al*, 1989; Sundby & Schei, 1996], or were studies of infertility in a population of women who had recently delivered and therefore only resolved infertility could be estimated [Ghazia *et al*, 1991]. These four studies were not included in table 1.3.2 because of the potential for bias in the estimates related to the primary purpose and thus methods of the study in which the data were collected.

Table 1.3.2: Summary of seven non-British population based studies which have estimated the occurrence of infertility

Author Year of publication Country	Respondents Response (%)	Age range Year of study	Risk* of any infertility (%)	Risk* of primary infertility (%)	Risk* of secondary infertility (%)	Risk* of primary infecundity (%)	Risk* of secondary infecundity (%)	Risk* of voluntary childlessness(%)
Infertility defined by a one year cut off:								
Rachootin & Olsen 1981 & 1982 Denmark	709 74%	25-45yrs 1979	**	16.1%	16.6%	4.0%	4.2%	7.3%
Poston & Kramer 1983 USA	2586 † 3215 †	30+yrs 1970 30+yrs 1973	** **	** **	** **	2.7% 2.6%	** **	2.2% 1.6%
Mosher 1985 USA	6482 † 3551 †	15-44yrs 1976 15-44yrs 1982/83	14.3% 13.9%					
Hirsch & Mosher 1987 USA	5855 †	15-44yrs 1976 & 82	18.9%	5.1%	13.8%	**	**	**
Webb & Holman 1992 Australia	1511 90.3%	16-44yrs 1988	19.1%	**	**	**	**	**
Schmidt *et al* 1995 Denmark	1905 76%	20-44yrs 1988	15.7%	**	**	**	**	**

* Life-time risk or reproductive life-time cumulative incidence ** Not estimated in this study † Not given

Table 1.3.2 contd: Summary of seven non-British population based studies which have estimated the occurrence of infertility

Author Year of publication Country	Respondents Response (%)	Age range Year of study	Risk* of any infertility (%)	Risk* of primary infertility (%)	Risk* of secondary infertility (%)	Risk* of primary infecundity (%)	Risk* of secondary infecundity (%)	Risk* of voluntary childlessness(%)
<u>Infertility defined by a two year cut off</u>:								
Rachootin & Olsen 1981&1982 Denmark	709 74%	25-45yrs 1979	16.1%	8.9%	9.0%	**	**	7.3%
Högberg *et al* 1992 Sweden	4299 87%	20-44yrs 1981	**	6.6%	11.0%	**	**	**

* Life-time risk or reproductive life-time cumulative incidence ** Not estimated in this study † Not given

Using the weighted average estimates the combined results of the five British population based studies by Page [1989], Greenhall & Vessey [1990], Templeton *et al* [1990,1991], Gunnell & Ewings [1994] and Buckett & Bentick [1997] can be summarised thus:

Using the definition of infertility based on a one year period:

1. 1 in 4 (23.6%) women will experience an episode of infertility at some stage in their reproductive life.
2. 1 in 7 (13.8%) women will experience difficulty conceiving their first pregnancy (primary infertility).
3. 1 in 7 (14.0%) women will experience difficulty conceiving their second or subsequent pregnancy (secondary infertility).

Using the definition of infertility based on a two year period:

4. 1 in 7 (13.4%) women will experience an episode of infertility at some stage in their reproductive life.
5. 1 in 12 (8.1%) women will experience primary infertility.
6. 1 in 16 (6.2%) women will experience secondary infertility.

Overall:

7. 1 in 38 (2.6%) women will never deliver a desired first child, that is they will have primary infecundity and be involuntarily childless.
8. 1 in 26 (3.8%) women who have had one or more children already will not be able to have a further desired child and will have secondary infecundity.
9. 1 in 12 (8.1%) women are voluntarily childless.

1.3.3 Presentation for treatment and the resolution of infertility

A discussion about the occurrence of infertility would be incomplete without consideration of the presentation for treatment. The need and demand for any medical treatment is in part dependent upon supply and accessibility of treatment services [Donaldson & Donaldson, 1993]. Both of these factors vary enormously across the globe. For this reason the discussion relating to the presentation for investigation and treatment of infertility will be confined to British data. Of course, that is not to deny that even within the UK variations in service need, demand, supply and accessibility also exist. It is also clear that the demand for infertility treatment has increased in recent years [Page, 1988] such that it should be noted that the estimates of service demand reviewed and presented here relate to the 'historical' experiences of the populations of women surveyed and are only likely to be indicative of future service demand.

Three of the population based studies [Templeton *et al*, 1990, 1991; Gunnell & Ewings, 1994; Buckett & Bentick, 1997] estimated the reproductive life-time risk of presenting to a General Practitioner (GP) for the investigation and treatment of infertility. These estimates ranged from 8.4% to 13.0%. The combined weighted average risk (weighted directly by sample size) was 11.5% (95%CI 10.6%, 12.4%). Four of the studies estimated the risk of presenting for a specialist opinion [Page, 1989; Templeton *et al*, 1990, 1991; Gunnell & Ewings, 1994; Buckett & Bentick, 1997]. Given the difficulties with denominator definition the work of Hull *et al* is not included here [Hull *et al*, 1985]. The estimates from the four studies ranged from 5.9% to 10.5%; the combined weighted average risk was 8.1% (95%CI 7.4%, 8.9%).That is to say, from these estimates, 1 in 9 women will, at some stage in their reproductive life present to their GP complaining of infertility and 1 in 12 women will be referred for a specialist opinion.

For those women with primary and secondary infertility defined on the basis of the one year definition of infertility Greeenhall & Vessey [1990], Gunnell & Ewings [1994] and Buckett & Bentick [1997] estimated the proportion of women who eventually conceived, regardless of whether or not they received treatment. The estimates for the proportion conceiving after primary infertility ranged from 68.1% to 86.3%, with a combined weighted average of 82.6% (95%CI 79.0%, 85.7%). For secondary infertility the estimates ranged from 60.4% to 80.1%, with a combined weighted average of 74.5% (95%CI 70.5%, 78.2%). That is to say, from these estimates, over 8 in every 10 women with primary infertility and over 7 in every 10 women with secondary infertility are likely to conceive. It should be noted however that since many of the women included in the samples would have been attempting to conceive during the 1960s and 1970s, with the improved treatments now available these proportions are likely to under estimate the current chances of conception.

Templeton *et al* [1990, 1991] and Gunnell & Ewings [1994] estimated the proportions eventually conceiving based on the definition of infertility with two years attempted conception. As expected these estimates were lower than those based on one year of infertility, since they would by definition, include women with more refractory infertility and would include a greater proportion of women who would never go on to conceive. However, for reasons which are not clear the two sets of estimates based on the two year definition were vastly different to each other. Templeton *et al* estimated that 41.6% of women with primary infertility would eventually conceive compared to 73.1% estimated by Gunnell & Ewings. For secondary infertility the proportions were 15.4% and 63.6% respectively. Thus, given the wide and unexplained variation it would be inappropriate to attempt to estimate a combined value.

In summary, whilst these data are likely to underestimate the current situation, they are the best estimates presently available. These data indicate that:

1. 1 in 9 (11.5%) women will, at some stage in their reproductive life, present to their GP complaining of infertility.
2. 1 in 12 (8.1%) women will be referred for a specialist opinion.
3. Over 8 out of 10 (82.6%) women with primary infertility based on the one year definition will eventually conceive.
4. Over 7 out of 10 (74.5%) women with secondary infertility based on the one year definition will eventually conceive.

1.4 PATHOPHYSIOLOGY OF MALE INFERTILITY

Successful conception requires the orchestration of a series of highly complex physiological events in both the female and male partner. Spermatogenesis must result in the production of spermatozoa which, having been placed in the female reproductive tract, must have the capacity to traverse that tract, meet with a waiting ovum and fertilise the ovum in order to provide the paternal genetic material for fusion with the maternal contribution. A brief review of the anatomy and physiology of the male reproductive tract will provide a background to the discussion of the pathology of male infertility. This short review was written by reference to the publications of Jequier & Crich [1986], Dixon [1980], de Kretser [1995], the work edited by Lipshultz & Howards [1991] and an anonymous editorial in the British Medical Journal [Anon, 1979].

1.4.1 The anatomy and function of the male reproductive tract

Each testis is divided into a series of lobules in which the seminiferous tubules lie. The

development and production of spermatozoa takes place within these tubules. After passing through the rete testis spermatozoa empty into the epididymis. The long epididymal duct plays a vital role in sperm maturation and storage. The vas deferens emerges from the epididymal duct and after its course through the inguinal canal it dilates behind the bladder to form the ampulla. On each side, left and right, the duct of the seminal vesicle joins the ampulla and the secretions of the seminal vesicles together with prostatic secretions make up a large portion of the seminal fluid. The junction of the ampulla and seminal vesicle forms the ejaculatory duct on each side, which then opens into the prostatic section of the urethra.

1.4.2 Spermatogenesis

In common with the ovary the testicle has two primary functions. First, is the production of hormones, particularly testosterone, by the Leydig cells which lie in the connective tissue between the seminiferous tubules. The second, is the production of spermatozoa. Spermatogonia are the basic stem cells which lie between the Sertoli cells of the seminiferous tubules. At the start of the spermatogenic process, under hormone control, the spermatogonia increase their numbers by undergoing mitotic cell division to become primary spermatocytes. The primary spermatocytes undergo meiotic cell division to become secondary spermatocytes which then divide to complete the reduction division and become spermatids with a haploid chromosome complement at which point spermatogenesis is complete. Spermiogenesis takes place next, during which morphological changes occur and the spermatids differentiate into spermatozoa. The mature spermatids separate themselves from the Sertoli cells in the process of spermiation and enter the lumen of the seminiferous tubules as spermatozoa. The spermatozoa continue their maturation as they pass from the seminiferous tubules into the

epididymal duct where they acquire some degree of motility and the ability to penetrate and thus fertilise oocytes. The complete cycle of spermatogenesis and spermiogenesis in man takes approximately 70 days in the testis with another 7 to 21 days of maturation in the epididymis.

1.4.3 Ejaculation and fertilisation

Erection results from parasympathetically induced distention of the vascular spaces of the penis. Ejaculation is under dual autonomic control with the initial delivery, or emission, of the various components of the semen to the urethra by sympathetic nervous stimulation of the muscles in the walls of the vas deferens, seminal vesicles and prostate. The parasympathetic reflex causes tonic-clonic contractions of the bulbo-cavernosus muscles of the penis which results in the expulsion, or ejaculation, of the semen. At the same time the sympathetic reflex closes the internal urinary sphincter to avoid retrograde ejaculation into the bladder. The ejaculate should contain several million motile and normally formed spermatozoa.

During sexual intercourse semen is deposited into the vagina. Following liquefaction of the semen the fully motile spermatozoa make their way through the cervix and into the uterus where the process of capacitation starts in preparation for fertilisation. Provided that intercourse has taken place during the appropriate phase of the ovarian cycle the spermatozoa will meet the waiting mature ovum in the oviduct (Fallopian tubes) and fertilisation by a single spermatozoon will occur. This involves the penetration of the zona of the ovum and the combination of the two nuclei with their respective haploid chromosome complement to form a single diploid nucleus. Cell division follows and the developing embryo or blastocyst moves down the Fallopian tube into the uterus and

implantation and placentation follow. The chorion of the blastocyst produces human chorionic gonadotrophin, the β sub-unit of which (β-hCG) can be detected in maternal serum. Using a measure of β-hCG a so-called 'biochemical' diagnosis of pregnancy, in contrast to a clinical diagnosis, can be made. A diagnostic rise in the level of β-hCG can be detected prior to the first missed menstrual bleed.

1.4.4 Pathology associated with male infertility

The relative contributions of male and female pathology to the pathogenesis of infertility is difficult to assess and is likely to vary due to the differing incidence of aetiological factors in different populations. Furthermore, any such assessment will necessarily depend upon the extent of the investigations carried out which in turn will depend on the available resources and expertise. In addition, since such assessments have largely been carried out in specialist infertility clinics, the impact of the extent of investigation and treatment in the primary care setting (GPs) is also likely to affect the apparent relative male and female contributions estimated. Female factors are more likely to be treated by GPs, *eg* anovulation, than are male factors.

Male factors which contribute to infertility are variously quoted as affecting from 26% [Hull *et al*, 1985], 42% [Schmidt *et al*, 1995] to 50% of couples [Jaffe & Jewelewicz, 1991]. Probably the largest study ever conducted to quantify the pathology associated with infertility was the WHO Task Force Standardized Investigation of the Infertile Couple [Farley, 1987]. The findings from 5,713 infertile couples are illustrated in table 1.4.1 and can be summarised thus: in 14.1% of infertile couples both partners had normal findings; in 23.5% of couples male factors were the sole abnormal findings; in 35.2% female factors were the sole abnormal findings; and in 27.2% there were abnormal findings in both

partners. That is to say, male factors contributed to couple infertility in 50.7% of couples and female factors contributed in 62.4%, with the overlap of both male and female factors present in 27.2% of couples.

Table 1.4.1: The relative contributions of male and female factors in 5,713 infertile couples [Farley, 1987]

Female findings	Male findings		
	Normal	Abnormal	Total
Normal	14.1%	23.5%	37.6%
Abnormal	35.2%	27.2%	62.4%
Total	49.3%	50.7%	100%

The three commonest female diagnoses associated with couple infertility in the developed world are 'no demonstrable cause', anovulation and tubal blockage [Farley, 1987]. Concentrating now on just the pathology associated with male infertility, this can be divided into four main groups, although the examples given within each group do not provide an exhaustive list [ACOG, 1991; Baker & Keogh, 1994; de Kretser, 1994, 1997].

1. Disorders of spermatogenesis which may be pretesticular or testicular in origin. The pretesticular problems include hypothalamic or pituitary disorders which interfere with the function of the hypothalamic-pituitary axis; other hormone disorders; and chromosomal abnormalities such as Klinefelter Syndrome. Recently added to this list are micro deletions on the Y chromosome. The testicular problems include mumps orchitis, cryptorchidism, hypospermatogenesis, varicocele and chemical or radiation injury.

2. Obstruction in the efferent duct system results from congenital problems such as congenital bilateral absence of the vas and ejaculatory duct obstruction. Acquired causes include infections, which may cause scarring along any portion of the efferent duct system, and vasectomy.
3. Disorders of sperm motility can also be congenital or acquired. Congenital causes include the immotile cilia syndrome, epididymal dysfunction resulting in disordered sperm maturation, and varicocele. Acquired causes include infections, antisperm antibodies, infrequent ejaculation and the use of certain drugs.
4. Sexual dysfunction may result from anatomical disorders such as uncorrected hypospadias and bladder exstrophy. Ejaculation abnormalities include retrograde ejaculation into the bladder, and premature and retarded ejaculation, all of which may have a central nervous origin. Impotence may be organic or psychogenic in origin.

Baker and Keogh [1994] also make the point that in the future such lists may also include pathology related to the function of sperm once in the female genital tract, beyond simply motility, and might include such defects as zona binding and penetration defects.

The frequency of occurrence of the different diagnoses found in the male partner is again difficult to quantify and is necessarily dependent upon the extent of investigations which in turn depends upon the available resources and expertise. It is also likely to vary in clinical series due to variations in case-mix seen in different clinical settings, variations in the underlying incidence in different populations and the contribution of GPs to the management of infertility.

The distribution of diagnoses of male infertility from five clinical series from 1956 to 1986

was reviewed by Baker *et al* [1986]. The series ranged in size from 360 to 1294 men. Disorders of spermatogenesis accounted for 10.5% to 18.6% of cases; obstruction of the efferent duct system (including vasectomy) accounted for 0% to 7.4%; disorders of motility affected 0% to 1.3%; sexual dysfunction 0% to 7.1%; other causes were given for 0% to 60.5%; and no demonstrable cause was found in 5.4% to 79.2%. The 'other' category included a variety of diagnoses including varicocele which alone accounted for 9.2% to 37.4% of diagnoses.

The WHO Task Force on the Diagnosis and Treatment of Infertility reported on 3,438 men from infertile couples [Rowe & Darling, 1984]. They found disorders of spermatogenesis accounted for 18.8% of diagnoses; obstruction 5.8%; disorders of motility 18.4%; sexual dysfunction 1%; other causes 18.5%; and no demonstrable cause 48.3%. The single commonest diagnosis was varicocele (categorised under 'other' in this classification) which was present in 17.2% of cases and was only diagnosed when a varicocele was present together with abnormal semen parameters.

A number of drugs and toxins are known to impair the many stages of the delicately balanced process of conception. For example, a technical bulletin from the American College of Obstetricians and Gynaecologist lists 26 groups of drugs and toxins which may have adverse effects on male reproductive function [ACOG, 1991]. Examples from this list include chemotherapeutic agents and radiotherapy which cause germ cell depletion. Alcohol which is a testicular toxin can impair spermatogenesis and it can also cause pituitary suppression. Major tranquillizers can cause impotence (organic) and ejaculatory dysfunction, whilst narcotics and minor tranquillizers can lead to decreased libido and impotence. Proponents of the view that sperm counts have fallen in recent decades

hypothesise that this may be due in part to exposure to environmental oestrogens which have an antiandrogenic effect and thus interfere with spermatogenesis [Sharpe, 1993].

From this short review it is clear that conception is a highly complex process with many steps each of which may be susceptible to the effects of adverse exposures.

1.5 ROLE OF OCCUPATION IN THE AETIOLOGY OF INFERTILITY

A relationship between health and occupation was documented by Hippocrates in the fifth century BC [Hippocrates, 1938]:

> "Whoever wishes to investigate medicine properly should proceed thus: in the first place to consider ..... the mode in which the inhabitants live, and what are their pursuits, whether they are fond of drinking and eating to excess, and given to indolence, or are fond of exercise and **labour**."

In 1700 Bernardino Ramazzini published the first systematic review exploring the subject of occupationally related disease which was entitled *De Morbis Artificum* (Diseases of Workers) [Ramazzini, 1964]. Ramazzini, who is regarded as the father of occupational medicine, noted the excess risk of breast cancer experienced by Nuns and correctly suggested that this related to their celibate lifestyle rather than other specific occupational exposures. Ramazzini also made reference to the possible adverse effects of occupation upon reproductive function in relation to ailments of the breast suffered by wet nurses and the fatiguing work of weavers " .... for if pregnant they easily miscarry and expel the fetus prematurely ..." [Ramazzini, 1964].

The role of the adverse exposures associated with occupation in the aetiology of disease has been most extensively studied in the area of cancer [Checkoway *et al*, 1989]. Potts

described the first direct connection between an occupational exposure and the risk of a specific cancer in 1775 when he noted the association between chimney sweeping and cancer of the scrotum [Checkoway *et al*, 1989]. With the post World War II developments in epidemiological techniques occupational exposures became a fruitful area of research and consequent disease control. Such was the success of epidemiologists in the 1960s and 1970s in establishing the excess cancer risk for workers occupationally exposed to agents such as asbestos, benzene and benzidine dyes, that the possibility was raised that cancer overall might be due largely to workplace exposures [Cullen *et al*, 1990]. Consequent upon more recent research this view has been modified somewhat and newer estimates of the burden of cancer related to workplace exposure in the USA have ranged from a more modest four to 10 percent [Cullen *et al* 1990].

Studies of occupational exposures provide valuable data in relation to the risks for specific workers. In addition they also provide a means of identifying and studying the effects of exposure to ubiquitous substances *eg* benzene. Exposures in the workplace are often at higher levels than in the community, however, data from occupational groups can allow extrapolation to the wider community in the process known as risk assessment [Checkoway *et al*, 1989].

The adverse effects of certain chemicals and physical agents upon human reproduction have been recognised since antiquity. The abortifacient effects of lead were recognised by the Romans and are thought by some to have contributed to the decline of the Roman Empire [Gilfillan, 1965]; during the late nineteenth and early twentieth centuries women in the pottery and white lead industries also thought that lead was an abortifacient [Rom, 1976]. Nevertheless, despite these historical precedents the potential hazards of

occupational exposures upon human reproduction received little attention until the 1970s and early 1980s [MMWR, 1985].

The effects of thalidomide in the 1960s and methyl mercury poisoning that occurred in Minamata, Japan in the 1950s to 1970s focused attention on the teratogenic potential of chemical exposures. These disasters together with the increasing entry of women into the work force directed attention to the potential hazards of workplace exposures on female reproductive function. However, it was not until 1977 with the publication of the work by Whorton *et al* [1977] concerning male infertility and sterility following occupational exposure in the production of the nematocide 1,2-dibromo-3-choloropropane (DBCP) that the impact of work upon male reproductive function was really considered [Wyrobek *et al*, 1983]. Prior to this, paternal occupation was largely regarded as simply an indicator of socio-economic status [Emanuel & Sever, 1973].

The perceived central role of the female in the aetiology of infertility is reflected in the volume of literature devoted to this topic in contrast to the volume devoted to the male role. This is similarly reflected in research in the area of occupation and reproductive function, although, it probably also reflects the relative ease of reproductive outcome measurements in women compared to men [Schrag & Dixon, 1985]. A plethora of reproductive outcomes have been investigated with respect to occupational exposures of women. This is illustrated in the review by Rosenberg *et al* [1987] of English-language publications between 1981 and 1985. The authors located 92 articles dealing with occupational influences on reproduction. In these 92 papers 108 reproductive outcomes were investigated, of these, 72 were adverse pregnancy outcomes related to female occupation, compared with only 21 which investigated occupation and male reproductive

function. Furthermore six of the 21 reported findings were related to exposure to DBCP. The remaining outcomes investigated were largely paediatric cancers.

Despite the political and social concerns relating to unemployment rates, in most modern industrialised societies exposure to work at some stage during adult life is still the norm. As such, particular occupations which adversely affect the fertility of individuals may potentially have a marked influence on the societal burden of infertility [MMWR, 1985].

1.5.1 Occupation and male infertility

Based on laboratory and clinical reports a relatively large number of therapeutic agents have been identified as adversely affecting male reproductive function; in contrast the list of chemical and other industrial agents is much shorter [Schrag & Dixon, 1985]. Compared with domestic animals human semen is of relatively poor quality and the role of industrial and environmental chemicals in producing this differential has been under scrutiny in recent years [Schrag & Dixon, 1985; Weeks *et al*, 1991; Sharpe, 1993].

Workplace exposures that may potentially adversely affect male reproductive function, other than chemicals, include physical agents such as altitude, temperature and radiation. Such effects might be direct, for example an elevated ambient temperature may adversely affect testicular function. There may also be an indirect effect, for example an elevated ambient temperature may increase the absorption of toxic substances by increasing lung ventilation and the circulatory rate.

Nevertheless, despite recent intensive efforts, the number of workplace chemical substances, physical agents and specific occupations for which there is evidence to

strongly support an adverse effect on male reproductive function are remarkably few [Weeks *et al*, 1991; Gold *et al*, 1994; Tas *et al*, 1996].

Tas *et al* [1996] reviewed 460 publications dealing with workplace exposures and adverse male reproductive function. They concluded that strong evidence of an adverse effect is available for only nine agents, namely heat, ionizing radiation, inorganic lead, manganese, mercury, DBCP, ethylene glycol ethers, carbon disulphide and welding. They also pointed out that evidence relating to many substances had simply not been sought or there was limited inconclusive evidence for some substances that had not been investigated further; that is to say, many other substances may have an adverse effect, but that evidence of this was not yet available. In their list of male reproductive toxicants Schrag & Dixon [1985] also included oestrogens; whereas the action of oestrogens was not included in the review by Tas *et al* [1996]. Weeks *et al* [1991] also included the action of chlordecone (an insecticide) in their list of agents, whereas Tas *et al* considered that the available evidence relating to chlordecone was not strongly conclusive [1996].

For some of the identified agents there is a clearly identified mode of action, for some a biologically plausible pathway is suggested but not yet confirmed, whereas for others the mechanism of action is not known [Schrag & Dixon, 1985]. Some agents are also cytotoxic and some also carcinogenic, mutagenic and/or teratogenic. Yet as Schrag & Dixon [1985] point out probably the reproductive hazards of greatest importance are those which are subtle in action, do not have mutagenic or carcinogenic properties, are not cytotoxic and act by disrupting the physiological processes which are specific to reproduction.

As discussed in section 1.4 the physiology of male reproduction is highly complex and each of its stages may be susceptible to impairment. Occupational exposures may therefore theoretically have an adverse impact through several different mechanisms [Bonde *et al*, 1996]. They may be or act "as hormones or antihormones and interfere with the normal endocrine and paracrine regulation of testicular function; they may act as toxicants which destroy specific cell types including the germs cell, Sertoli cells or Leydig cells; they may act as germ cell mutagens leading to the production of sperm which are unable to fertilize or result in spontaneous abortions, birth defects or genetic disease in the offspring; or they may act as neurotoxic compounds affecting the sympathetic or parasympathetic control of erection, emission or ejaculation" [Bonde *et al*, 1996].

1.5.2 Hypothesis generation and aspects of study design

Identifying potential adverse workplace exposures and then investigating their effects is not without difficulty. Many workers are not aware of the potential adversity in the conditions surrounding them or the substances they handle; they are rarely exposed to only one chemical agent which makes it difficult to single out one particular reproductive toxin; many people change job and forget the details of their previous employment conditions; job title which is frequently used as a proxy for occupational exposures is often not a sensitive measure of actual exposure; and conversely a particular exposure may be prevalent in occupations with many different titles or duties [Schrag & Dixon, 1985].

However, probably the greatest problem facing investigators who wish to elucidate occupational causes of male reproductive dysfunction is the relative absence of plausible hypotheses to test; with no easy method of generating such hypotheses. The occupational epidemiologist is surrounded by a plethora of potential toxicants together with a range of

reproductive outcomes. Nevertheless, the rational development of hypotheses is difficult [Hogue, 1986].

Animal data can provide some clues, but even then available data on the impact of industrial chemicals and physical agents on animal reproductive function are very limited, particularly when the interest is primarily *male* reproductive function. For example, of the 104,000 chemical and physical workplace agents listed by the National Institute for Occupational Safety and Health Registry of Toxic Effects of Chemical Substances in the USA, over 95% have not had the effects on reproduction assessed in any form, be it animal or human [Gold *et al*, 1994]. Furthermore, there are data which suggest that some chemicals can impair male human fertility at exposure levels that do not detectably affect rat spermatogenesis [Bonde *et al*, 1996].

Descriptions of disease using time, place and person descriptors of vital statistics and other easily accessible data together with ecological correlation studies are standard approaches to hypothesis generation in epidemiology. However, these approaches are of little use in the workplace and reproduction field, especially male reproduction. This is simply because the data to carry out such descriptive work are extremely limited. The nearest such analyses have been those relating to changes in sperm concentration over time. However, these studies led to controversy over their validity and interpretation. In particular, they generated speculation as to their meaning (if indeed the changes are real) and very wide ranging, non-specific hypotheses about 'environmental' toxins [Carlsen *et al*, 1992; Sharpe, 1993; Auger *et al*, 1995; Comhaire *et al*, 1995; Irvine *et al*, 1996; Bromwich *et al*, 1994; Olsen *et al*, 1995; Bujan *et al*, 1996; Vierula *et al*, 1996; Lipshultz, 1996; Fisch *et al*, 1996; Paulsen *et al*, 1996; Fisch & Goluboff, 1996; Pajarinen *et al*,

1997]. Certainly little has emerged from these analyses that could be tested directly in the workplace.

Data sets collected to test other hypotheses can, if 'trawled', be used to identify other hypotheses. However, this approach is not a notable feature of the occupational disease and reproductive dysfunction literature.

Studies of clinic populations of patients with infertility have been investigated with regard to current occupation with the intention of generating hypotheses. However, given the wide range of occupations described and the limited power of most studies, few testable hypotheses have emerged [Henderson *et al*, 1986; Buiatti *et al*, 1984; Collins *et al*, 1993]. One notable exception to this was the emergence of the hypothesis relating to welding which came from clinic based population studies and has subsequently been the focus of extensive primary hypothesis testing [Rachootin & Oslen, 1983; Lindbohm *et al*, 1984; Mortensen, 1988; Bonde, 1993].

The DBCP story emerged because of the observations of the workers themselves (mostly young men) who had noted that few of them had fathered a child in recent years. One worker persuaded five of his colleagues to undergo a semen analysis test and all had grossly abnormal results. These findings were sent to Donald Whorton the Union Consultant who instituted a wider, formal investigation [Whorton, 1982]. The results from this and later studies confirmed the worker's suspicions of the testicular toxic effects of DBCP, which, as it turned out, were reversible for only some of the workers [Whorton *et al*, 1977; Whorton *et al*, 1979; Glass *et al*, 1979; Egnatz *et al*, 1980; Kharrazi *et al*, 1980; Milby & Whorton, 1980; Lantz *et al*, 1981; Landrigan *et al*, 1983; Eaton *et al*, 1986; Olsen

et al, 1990; Thrupp, 1991]. A further interesting feature of the DBCP story was the existing volume of animal data which could have predicted its adverse impact on human male reproductive function. As early as 1961 Torkelson *et al* and Kodama *et al* jointly published the findings from two independent studies of the effects of DBCP exposure on rats [Torkelson *et al*, 1961]. These studies demonstrated the toxic effects of DBCP on the liver, kidneys and testicles. Testicular atrophy was present even at the lowest exposure level tested. The histological testicular changes were noted to include "degenerative changes in the seminiferous tubules, an increase in Sertoli cells, reduction in the number of sperm cells, and abnormal forms of sperm cells" [Torkelson *et al*, 1961].

Anecdotal reports and clinical observation, which may or may not be reported as case reports or case series, often provide a starting point for epidemiological investigations in general. Such was the case with the hypothesis tested in the work presented in this thesis. In 1988, a Leicestershire Gynaecologist wrote to the District Medical Officer reporting that a small number of men working in the boot and shoe industry had attended his clinic with their wives complaining of difficulty conceiving; subsequent investigations showed them to have oligozoospermia (low sperm concentration). This raised the question of whether leatherwork poses a hazard to male fertility.

Interestingly, previous work in Leicestershire had found leatherworkers (female workers in the boot and shoe industry) to be at an increased risk of experiencing a perinatal death [Clarke & Mason, 1985]. The excess risk was largely associated with lethal birth defects and macerated stillbirths and a two fold excess risk remained even when the leatherworkers were compared to other manual workers in the same social class. McDonald & McDonald [1986] examined their cohort of 56,012 women to test the

hypothesis raised by the Leicestershire data. They found that leatherworkers had a significant, nearly three fold, excess of stillbirths without birth defects. Clarke & Mason [1988] then investigated their cases and controls further and found that leatherworkers who had experienced a perinatal death had had fewer pregnancies in the past compared to leatherworkers who had had a live birth and other social class III manual workers who had had either a live birth or perinatal death. Other potential confounding factors were not adjusted for. The authors concluded that women working in the boot and shoe industry may have been exposed to a fetotoxic agent.

The finding of Clarke and Mason in relation to fewer conceptions suggests that either very early fetotoxic effects prior to the first missed period, or toxic effects on ovulation, fertilization or implantation were occurring. It is interesting to note that an investigation in Finland looking at spontaneous abortions in women who were members of the Rubber and Leather Workers Union did not demonstrate an excess of spontaneous abortions in leatherworkers [Hemminki *et al*, 1983]. Whereas, recently, Agnesi *et al* [1997] found an increased risk of spontaneous abortion in women working in shoe manufacturing in Northern Italy.

1.6 SUMMARY OF THE BACKGROUND

In summary, infertility is a distressing condition. Contrary to popular belief it is a relatively common experience in modern industrialised societies. There are many inherent difficulties in the investigation of infertility, not least of which is the absence of a clear, agreed nomenclature with which to define the condition. The process of conception is a highly complex series of socio-biological events involving two people. Its many delicate stages render it particularly susceptible to dysfunction inducing agents. Despite a considerable research effort few male reproductive toxins have been identified in the workplace. Part of the difficulty of investigation in the field of occupationally related male infertility is the relative lack of hypotheses to test.

AIMS

2.1 BACKGROUND

In 1988, a Leicestershire Gynaecologist wrote to the District Medical Officer reporting that a small number of men working in the boot and shoe industry had attended his clinic with their wives complaining of difficulty conceiving; subsequent investigations showed them to have oligozoospermia (low sperm concentration). This raised the question and the hypothesis to be tested by this study, of whether leatherwork poses a hazard to male fertility.

2.2 THE HYPOTHESIS

This study was primarily designed to test the hypothesis that leather work is associated with male infertility, mediated through the development of oligozoospermia. The basis of any association was thought, *a priori*, to be with exposure to the solvents used in leatherwork, rather than exposure to the leather itself or to leather substitutes.

The secondary aim of the study was to produce a data set from which hypotheses relating to other possible occupational causes of infertility may be generated and upon which other independent hypotheses may be tested.

2.3 THE OBJECTIVES

2.3.1 Objectives relating to the primary hypothesis

In order to test the primary hypothesis the following objectives were defined. To test the hypotheses that:

(i) Leatherwork is associated with an increased risk of presenting for the

investigation of infertility

(ii) Work with solvents is associated with an increased risk of presenting for the investigation of infertility

(iii) Leatherwork is associated with an increased risk of presenting with oligozoospermia

(iv) Work with solvents is associated with an increased risk of presenting with oligozoospermia

2.3.2 Objectives relating to the secondary aims

In order to meet the secondary aims of the study the following objectives were defined. To test the hypothesis that:

(i) Leatherwork and work with solvents are associated with an increased risk of presenting with low sperm motility and high sperm deformity

(ii) Being a welder is a risk factor for presenting for the investigation of infertility and presenting with oligozoospermia, low sperm motility and high sperm deformity

Also:

(iii) To examine the data set in order to general new hypotheses relating to occupation and male infertility that can be investigated in future independent studies

METHODS

3.1 INTRODUCTION

Leicestershire is a pleasant, predominantly rural county situated in central England. The county has six main centres of population, each separated from the other by tracts of rolling countryside and picture post-card villages. The City of Leicester is situated in the heart of the county with the market towns dotted peripherally. Economically relatively prosperous, the traditional major industries in Leicestershire are hosiery and shoe manufacture, farming, light engineering and coal mining.

In 1991 the population of Leicestershire was estimated at the census to be 867,521 [OPCS, 1992a]. The geographical distribution of the population within the county is, however, uneven. Approximately 320,000 people live within the City of Leicester itself and roughly one half of the entire county population live within five miles of the city centre. The ethnic populations of Leicestershire are of interest both for the cultural richness that they bring to the City and also because of the implications they have for health care provision. Census data show that about 25% of the City population are of 'Asian' ethnic origin, that is with ancestry from the Indian Sub-continent. A further 3% are from other ethnic groups, for example West Indian [OPCS, 1992a].

The boundary of Leicestershire Health Authority is co-terminus with that of the county. The major hospital services in the Authority are located in the city and there has been an increasing tendency to centralise all acute services.

The investigation reported here was designed as a case control study. The intended study population was all Leicestershire residents who presented as new referrals complaining of infertility to a general gynaecology or specialist infertility clinic in Leicestershire between November 1988 and November 1991. It was anticipated that during this period of time 2,000 couples would be eligible to participate. Although the primary hypothesis related to male infertility, data were collected from both the male and female partners of presenting couples.

3.2 THE DATA COLLECTION INSTRUMENTS

Two structured, interviewer administered questionnaires were designed; one for the male partner and one for the female partner of couples referred for the investigation and management of infertility. A copy of each questionnaire is included in appendix A.

The questionnaires were designed to collect the following information:

Personal identifying information;
Details about the interview;
Place of interview and which Consultant they were attending;
Age; Place of birth; Marital status;
The duration of time the couple had been together;

Details of the current occupation or most recent occupation for those unemployed at the time of interview;
Details of specific exposures in the current (or most recent occupation), namely: exposure to shift work, location of work, noise levels, cleanliness and temperature in the workplace; use of solvents, adhesives, cleaning agents, paint spraying, colour mixing solutions, photocopiers, micro-waves, ultrasound devices, ionising radiation and welding.
Details of all past occupations;
A specific question to elicit whether they had ever worked in the boot, shoe or leather industry was asked once the occupational history had been taken;
Details of all hobbies which used: solvents, glues, cleaning agents, paint spraying, colour mixing solutions or welding; Use of micro-wave ovens at home;

The general past medical history; specific questions asked about a history of mumps and a history of infertility investigations;
Current and past use of medications (including the oral contraceptive pill for women), both prescribed and over the counter purchases;

Coffee drinking;
Alcohol consumption;
Smoking history;

Past pregnancy history;
Duration of trying to conceive before referral for infertility investigations.

The questionnaires were constructed using previously validated questions when they were available. Where it was anticipated that comparisons with the Leicestershire Perinatal Mortality Survey (PNMS) control data would be made the questions used to collect the PNMS data were used in the infertility questionnaires.

An interviewer instruction manual was written to accompany the questionnaires. This gave instructions as to how the study was to be introduced to prospective participants and specific prompts for each question.

3.3 THE PILOT STUDY

Early versions of the questionnaires were informally piloted within the Department of Epidemiology and Public Health and as a consequence of the comments and criticisms received, draft pilot questionnaires were constructed. These questionnaires together with the administration procedure used in the clinics were piloted in the out-patient department on 18 men and 42 women during October and November 1988. As a consequence of this process, substantial changes were made to the order of the questions, although few changes were made to the content of questions. The flow and logical sequence of questions was thus improved. The data collected in the pilot study were not included in the final data set analysed.

3.4 INTERVIEWER TRAINING AND MONITORING

The interviewers were trained in both general interviewing techniques and specifically in relation to the questionnaire. Standardisation of data collection across the eight interviewers who interviewed at various stages as the study proceeded was maintained by the use of structured questionnaires, in conjunction with the detailed interviewer instruction manual and by periodic observation of interviews by another member of the study team. The data collection process was subject to a limited assessment of reliability (see section 3.6).

3.5 RECRUITMENT OF STUDY PARTICIPANTS

3.5.1 Eligibility criteria

In the first instance eligible participants were those Leicestershire resident couples, or individuals attending on their own, for their first appointment at any gynaecology or specialist infertility clinic in Leicestershire, with a new letter of referral for the investigation and management of infertility. The eligibility criteria were later expanded to include patients from Kettering (see section 3.5.4).

3.5.2 Patient identification

The majority of the patients eligible for inclusion attended the Leicester Royal Infirmary (LRI) or Leicester General Hospital (LGH) out-patients department. These patients were personally approached by the study staff in the out-patients clinic, an explanation as to the purpose and nature of the study was given and the couple was invited to participate in the study. The husbands/partners who had not attended clinic with their wives/partners were approached separately by letter and then contacted by telephone to arrange an appointment. The majority of these men were interviewed at home although a few were

interviewed at the next clinic appointment.

(i) Leicester General Hospital (LGH) - All referral letters to the gynaecology department at the LGH were reviewed prior to the out-patients clinic and details of the appointments for suitable referrals were noted. The interviewer thus attended the clinic only when suitable patients were due and so maximised work time efficiency.

(ii) Leicester Royal Infirmary (LRI) - At the LRI, the appointment making process did not allow a review of the letters of referral by study staff. New patients attending for the investigation of infertility were identified by the appointments clerk for each clinic and marked on the clinic appointment sheet. Details of suitable patients were collected from the clinic sheets one week prior to the clinic, again allowing the interviewer to attend clinic only when suitable patients were due.

(iii) Peripheral clinics - Patients attending peripheral clinics at Melton Mowbray, Hinckley Loughborough, Market Harborough and Oakham were identified by staff at each centre and details of suitable patients were sent by letter to the study staff. These patients were approached by an introductory letter and subsequent telephone call to arrange a mutually convenient appointment. If willing, these couples were interviewed at home.

(iv) Other clinics - A small number of Leicestershire patients attended hospitals outside Leicestershire and these patients were identified by contacting individual consultants in Nottingham, Nuneaton and Burton-On-Trent.

(v) Private patients - Specific access to private patients was not available although assurances were given by the clinical staff that all private patients were eventually seen in the hospital out-patients department prior to admission for investigations.

(vi) The safety net - The microbiology semen analysis database (see section 3.7) provided a safety net to identify eligible patients missed in the identification processes outlined above.

3.5.3 The interviewing procedure

Interviews for the main survey were carried out with new patients who attended clinic from the 14th November 1988 to the 30th September 1992. When conducted in the out-patients clinic the interviews were conducted in private and the male and female partners of each couple were interviewed separately. When home interviews were carried out the interviews were conducted separately and privately wherever possible. Information cards written in Hindi, Gujarati, Punjabi and Urdu were used to inform potential study participants, who spoke one of these languages but not English, about the nature and purpose of the study. In this situation a confidential medical translator service was used to interview willing non-English speakers.

3.5.4 Expansion of eligibility criteria - inclusion of patients from Kettering

At the design stage of the study, power calculations indicated that 2,000 men and 2,000 women would be need to be interviewed for the study to have sufficient power (see sections 3.9.3 and 3.9.4). At the outset of the study it was anticipated that 2,000 men and 2,000 women would be eligible for inclusion in the study over a three year period. These figures were estimated from discussion with clinical staff and a review of semen analysis

requests received by the microbiology laboratory in a three month period in early 1988. This review had also indicated that there would be a 50:50 split between samples having oligozoospermia and not having oligozoospermia. However, despite a high response to the study, recruitment did not meet the required target. A source of additional patients was thus sought. Northamptonshire which borders South Leicestershire had (and still has) an active boot and shoe industry and a single consultant in Kettering who sees all new infertility referrals to Kettering District General Hospital (DGH) at one clinic each week. It was decided therefore that the study would be expanded to include this source of patients. Interviewing at Kettering DGH commenced in August 1990. Details of all new private patient referrals seen by the consultant at the Woodlands Private Hospital in Kettering were also made available to the study interviewers. These patients were generally interviewed at home. The inclusion of Kettering patients greatly improved the patient recruitment into the study; although these patients were not included in all data analysis comparisons (see section 3.9.3).

3.6 THE RELIABILITY OF THE DATA COLLECTION

The reliability of the data collection process was subject to a limited assessment. Fifteen men and women agreed to be re-interviewed. They were re-interviewed between one and four months (mean 2.5 months, median 2 months) after their original interview. The re-interviews were conducted by the same interviewer in 11 cases and by a different interviewer in the remaining four. For each re-interviewee the contents of the two completed questionnaires were compared for each data item. For each interviewee the range of individual items was counted and the mean number and proportion of inconsistent items between the two questionnaires was calculated and the reasons for any inconsistencies were examined.

3.7 MICROBIOLOGY RESULTS DATABASE

The availability of the results of semen analyses were fundamental to the test of the primary hypothesis. During the course of the study the microbiology laboratory at the Leicester Royal Infirmary received semen specimens for analysis from all the clinics held in Leicestershire. The single exception to this was for those patients attending for *in vitro fertilisation* (IVF) and related procedures at the clinic set up at the Leicester Royal Infirmary in the final year of the study. However, the patients attending this clinic were not new infertility referrals and thus would not have been eligible for inclusion in the study.

The microbiology department carried out semen analyses in accordance with the World Health Organisation guidelines [WHO, 1987]. However, having completed the examination and having reported the result to the requesting doctor, the microbiology department did not include these results on their computerised results system and paper copies of the results were destroyed after three months. For this reason a semen analysis results database system was set up and run by the study staff for the duration of the study. The database was designed specifically for the study and written in D base III. The results of all semen analyses carried out for the purpose of the investigation of infertility were included on the database. Thus, when a couple had been interviewed their details were checked against the database and the results of the semen analysis were transferred to their questionnaires. The first two semen analyses performed on any one man were used so that any effects of treatment which may have been seen in later results would not be included.

The medical records of individuals without a result in the database were reviewed in order to identify absent results which may have been obtained from other sources *eg* hospitals

or doctors elsewhere, or to clarify ambiguities of identification due to insufficient personal details having been given on the semen analysis request form. A small proportion of results were obtained through this medical records review process.

In Kettering, semen analysis results were obtained from the medical records. At the end of the study outstanding results were obtained from the microbiology department, who kept and filed all their paper copies of results in alphabetical order of surname by the year the investigation was carried out.

3.8 DATA HANDLING

3.8.1 Data coding

The questionnaires were checked for completeness and then coded using the coding schedule designed specifically for the study. A copy of the coding schedule is included in appendix B. Current and all past occupational details were coded using the 1980 Office of Population Censuses and Surveys (OPCS) Classification of Occupations [OPCS, 1980]. Current occupations were also coded using the 1970 OPCS Classification of Occupations so that comparisons could be made with data from the controls in the Leicestershire Perinatal Mortality Survey (PNMS) as these data were coded using the 1970 edition [OPCS, 1970]. The data relating to illnesses, operations and drugs were coded using the Read Coding system [Read, 1989; O'Neil *et al*, 1995]. The data were double coded by two coders to ensure accuracy and standardisation across the five individuals who were involved in the coding process, although the double coding procedure was not blind.

3.8.2 Reliability of the data coding

The reliability of the data coding procedure was subject to a limited assessment. Firstly, an assessment of the reliability of the social class and socio-economic group coding was performed on the coding of the current occupation (or most recent occupation for those currently unemployed) using both the 1970 and 1980 editions of the OPCS Classification of Occupations [OPCS, 1970; OPCS, 1980]. The details of the current (or most recent) occupation from 60 questionnaires were blindly coded for a third time. The Kappa Statistic and percentage agreement between the initial and third coding were calculated for both occupational coding schemes. The reasons for any discrepancies were then examined.

Secondly, an assessment of the coding of two specific occupational groups, leatherwork and welding, was carried out using the original coding which had used both the 1970 and 1980 editions of the OPCS Classification of Occupations and had been coded by different people. The Kappa Statistic and percentage agreement were calculated. Differences between the coding by each occupational schedule were then examined. Following this examination a decision was made that all analyses involving the current (most recent) occupation would use the data as classified by the 1970 classification.

Finally, the reliability of the coding of occupation in general was assessed by comparing the coding of the current (or most recent) occupation for the 60 questionnaires which had been re-coded blindly using both the 1970 and 1980 classification schemes. The percentage agreement between the initial coding and the third coding was calculated for the 1970 classification of the occupational code and the industry code and the 1980 classification of the occupational code and the manual/non-manual variable. The reasons for any discrepancies were examined.

3.8.3 Data entry

A computer data entry module was written in Fortran to enable the data to be entered into flat ASCII computer data files for analysis. The data were entered twice by two separate people and the data files were then compared to identify data entry inconsistencies. The inconsistencies were then checked against the questionnaires and the error was corrected in the appropriate data file.

3.8.4 Data set cleaning

Once the data entry errors were resolved further data cleaning was carried out by generating cross tabulations of logically related variables in order to identify coding errors, inconsistencies and outlying data points. Potential errors were identified and resolved by reference once again to the questionnaires.

3.9 DATA ANALYSIS

The data analysis will be described firstly by outlining the primary and the secondary questions to be addressed, and the approach to undertaking these analyses and secondly by a description of the general analytical strategy.

3.9.1 The questions to be addressed by the primary analyses

The primary analyses carried out sought to address the following questions:

(i) Is leatherwork associated with an increased risk of presenting for the investigation of infertility ?

(ii) Is work with solvents associated with an increased risk of presenting for the investigation of infertility ?

(iii) Is leatherwork associated with an increased risk of presenting with oligozoospermia ?

(iv) Is work with solvents associated with an increased risk of presenting with oligozoospermia ?

Two main sets of case control comparisons were performed to address these questions and these are outlined in sections 3.9.3 and 3.9.4. The power calculations associated with these planned analysis determined the intended sample size of the study.

3.9.2 The questions to be addressed by the secondary analyses

The secondary analyses carried out sought to investigate:

(i) The relationship between leatherwork and work with solvents and a low sperm motility and a high sperm deformity proportion

(ii) Further analyses sought to use the data set to test an established hypothesis which related welding to male infertility [Rachootin & Olsen, 1983; Mortentsen, 1988; Bonde, 1993]

(iii) Finally, the data set was also examined in order to try to generate further hypotheses relating exposure to specific occupational groups with the risk of presenting for the investigation of infertility and the findings of abnormal semen results. The intention was that such hypotheses could then be tested in other existing data sets or future studies.

3.9.3 Design of set I of the case control analyses: Comparison with the Leicestershire PNMS control data

These analyses were designed to test the first two hypotheses that (i) leatherwork and (ii) work with solvents are associated with an increased risk of presenting for the investigation

of infertility.

For these purposes the exposures of interest, leatherwork and work with solvents, were defined *a priori* from the occupation job title of the current (or most recent) occupation as coded using the 1970 Classification of Occupations codes [OPCS, 1970]. The codes defining leatherwork are given in appendix C. Jobs involving work with solvents were defined by reviewing the literature. The job titles so defined together with their OPCS job codes are also given in appendix C.

The case group for these case control comparisons was defined as all 1606 Leicestershire resident men interviewed in the study, *ie* presenting for the investigation of infertility and excluding the Kettering derived participants and cross-boundary referrals. The control group for this comparison was obtained from the control population of the Leicestershire Perinatal Mortality Study (PNMS), on the basis that these data represent Leicestershire resident men who have fathered a child and thus are not infertile. The control population from the PNMS are a representative sample of all Leicestershire births [Clarke & Clayton, 1981]. Those controls with a history of infertility were excluded from the analysis in order to approximate 'normal fertility'; the analysis was then repeated including those with a history of infertility. Exposure information was derived from the parental details recorded in the PNMS; details about the fathers collected in the PNMS are, by necessity and the purpose of the PNMS, limited to occupational details only and are collected from the mother.

At the planning stage of the study, it was estimated that the prevalence of leatherwork in this control population (Leicestershire PNMS) was 13 per 1,000. The power calculation carried out indicated that for the analysis to have 90% power to detect a relative risk of 3.0

at the 5% level of statistical significance, the comparison groups should consist of 500 cases and 1,500 controls [Breslow & Day, 1987]. This would have involved using the entire control population of the PNMS from 1980 onwards. However, as the study progressed it became clear that the size and nature of the Leicestershire leather industry was changing quite dramatically. The recession during the late 1980s and early 1990s saw a marked decline in the number of people employed in the leather industry. Thus any comparisons with data from the early 1980s would almost certainly have resulted in an over estimate of the prevalence of current exposure to leatherwork in the control population. For this reason, the analysis was limited to the 1013 control fathers who did not have a history of infertility, from 1985 to 1992. Thus, the controls were derived from a similar time period to that of attempted conception for the infertility presenters.

3.9.4 Design of set II of the case control analyses: Oligozoospermia, leatherwork and work with solvents

These analyses were designed to test the hypotheses that (iii) leatherwork and (iv) work with solvents are associated with an increased risk of presenting with oligozoospermia.

For this purpose the exposures of interest, leatherwork and work with solvents, were defined *a priori* from the occupational job titles of the current and the past occupations. The codes defining these are given in the appendix D and were arrived at using a similar process as for the first set of case control analyses; the only difference being that the 1970 Classification of Occupation was used for the current (or most recent) occupation and the 1980 Classification of Occupation was used for all past occupations.

The male interviewees from the infertility study (including the Kettering participants) were

divided into cases and controls on the basis of their semen analysis results. Those men with a sperm concentration of 20 million per ml or less were defined as having oligozoospermia [WHO, 1987] and if oligozoospermia was present in both samples when two samples were tested and in the single sample when only one was available then these men were defined as the 'cases'. Those remaining, who had by definition a normal sperm concentration (above 20 million per ml) in at least one sample, were defined as the 'controls'. Those men for whom a semen analysis result was not available, those who had never worked (and thus could never have been exposed to particular occupations) and those who had substantial amounts of missing data were excluded from this part of the analysis. In total, on this basis, 326 men were excluded and 1580 were included.

Other variables of interest in these analyses included medical conditions, operations and treatments. Given the wide range of medical conditions and drugs reported this information was dealt with by grouping it into binary terms as follows. The details of all medical conditions and operations reported were classified by reference to the Oxford Textbook of Medicine and a textbook on male infertility [OTM, 1996; Lipshultz & Howards, 1991] into conditions which may or may not potentially impair male fertility by virtue of the pathogenesis of the disease or its treatment. This list is given in appendix D. Information about current and past medication use were classified by reference to the British National Formulary [BNF, 1992] into those drugs that may and those that are unlikely to impair male fertility (appendix D).

The power calculation carried out in the design stage indicated that for these analyses to have 90% power to detect a relative risk of 3.0 at the 5% level of statistical significance, the comparison would need to be based upon 1,000 cases and 1,000 controls [Breslow &

Day, 1987]. Given that the pilot work indicated that the split of oligozoospermia to a normal sperm concentration was 50:50 the target sample size for interview was thus 2,000 men (and their partners).

3.9.5 Design of the other case control comparisons

For the other comparisons which related to low motility and high deformity, cases and controls were again defined on the basis of the semen analysis results. Cases with low motility were those men who were found to have 50% or less motile sperm [WHO, 1987] in both samples when two samples were tested or in the single sample when only one was tested. Controls were those remaining men who, by definition, had normal sperm motility in at least one sample. Cases with high deformity were those men who were found to have 70% or greater deformed sperm [WHO, 1987] in both samples when two samples were tested or in the single sample when only one sample had been tested. The controls were the remaining men who, by definition, had a sperm deformity proportion of less than 70% in at least one sample.

Again these analyses were based on 1580 men who had at least one semen sample available, had worked at some stage and had few missing data. Exposure categories were defined on the basis of the occupational categories given in appendix C.

3.9.6 The general analytical strategy

In general throughout the analysis, statistical inferences were drawn on the basis of odds ratio estimates or the change in semen parameter estimates and their 95% confidence interval. This was in preference to the calculation of P values from statistical significance testing alone. A statistically significant result at the $P<0.05$ level was inferred from the 95%

confidence interval for an odds ratio when the interval did not include the value one. Given that case control analyses were performed odds ratios were used to estimate relative risk.

(i) Comparisons with the perinatal controls - For the comparisons between the perinatal mortality survey controls and the infertility presenters, unadjusted odds ratios (ORs) were estimated and 95% confidence intervals (95%CIs) calculated using the method described by Clayton & Hills [1993]. As confounder data were not available from the perinatal controls (occupational information was the only information available about the fathers) adjusted analyses could not be performed.

(ii) The logistic regression analysis - For the 'within infertility presenter' analyses, that is the analyses based on the infertility study participants alone, the same general analytical strategy was used for all the analyses. Using case and control status based on the binary division of the semen results, comparisons were made between the exposures to the different occupational groups of interest. Univariate analyses to produce unadjusted odds ratio estimates were carried out using unconditional logistic regression performed in S-Plus [S-Plus, 1993]. Two strategies for each set of the adjusted analyses were used. First, a parsimonious, statistically rational multiple logistic regression model was produced by including all potential confounding variables as categorical or binary terms in the model and removing each term one by one. The criterion which determined whether terms could be removed from the model was the conventional likelihood ratio test. In other words twice the change in log likelihood *ie* the change in the deviance, compared to the Chi-squared distribution on the change in degrees of freedom commensurate with the term removed on each occasion. This was one degree of freedom for the binary terms and (n-1) for categorical terms with (n) categories. The terms were removed in ascending order of the

likelihood ratio test and all terms that did not represent a statistically significant ($P<0.05$) component of the model were removed. Once the model contained only those terms which made a statistically significant contribution to the model the need for interaction terms was assessed. In view of the multiple significance testing involved, statistical significance was set at $P<0.01$ for this part of the modelling.

The terms included as potential confounding variables for current occupational exposures were:

History of mumps; included as a binary (b) term
Illnesses (appendix D) (b)
Operations (appendix D) (b)
Medicines - current (appendix D) (b)
Medicines - past (appendix D) (b)
X-ray of the pelvis or abdomen (b)
Current alcohol consumption; included as a categorical (c) term
Current caffeinated coffee or cola consumption (b)
Current smoking habits (c)
Currently working or not (b)
Leicestershire resident status (b)
Age group (c)
Marital status (b)
Social class (III versus the rest) (b)
Work rota (b)
Noise level at work (b)
Location of work (b)
Cleanliness of place of work (b)
Ambient temperature of place of work (b)
Solvent use at work (b)
Adhesive use at work (b)
Use of cleaning agents at work (b)
Paint spraying (b)
Use of colour mixing solutions (b)
Use of a photocopier (b)
Use of a visual display unit (VDU) (b)
Use of a microwave at work (b)
Welding at work (b)
Solvent use at home (b)
Adhesive use at home (b)
Cleaning agent use at home (b)
Paint spraying use at home (b)
Welding at home (b)
Microwave use at home (b)

When the exposure was *ever* having had that occupation *eg* ever leatherwork, then the potential confounders examined were those listed above from a history of mumps to social class inclusive. The others were not included as they specifically related to the current (or most recent) occupation.

The second approach to the modelling involved the construction of 'biologically rational' models. These models included terms for which were there were good *a priori* biological or clinical grounds for viewing them as confounders regardless of their apparent effect in the present study. All of these terms were included in each model and no exclusion process was undertaken. The terms included in the 'biological' models were:

Illnesses (appendix D); included as a binary (b) term
Operations (appendix D) (b)
Medicines - current (appendix D) (b)
Medicines - past (appendix D) (b)
X-ray of the pelvis or abdomen
Leicestershire resident status (b)
Age group; included as a categorical (c) term
Social class (III versus the rest) (b)

(iii) Probability calculations for small odds ratios and 'negative' results - Most of the results found in this study showed a small adverse effect of exposure, that is a small odds ratio greater than one, or a protective effect *ie* an odds ratio less than one. Most of the results were not statistically significant. In order to make sensible inferences with such results the probability that the true relative risk was as great or greater than, or less than certain threshold values was calculated. The threshold values 2.0 or greater and the value 0.5 or less were chosen as they were thought to be odds ratios which would reflect an effect of clinically important magnitude which was worth observing. Based on the odds ratios observed and using the Bayesian method described by Burton [1994] the

probabilities that the true relative risk was 2.0 or greater or 0.5 or less were estimated for each of the exposure outcome relationships investigated. The probabilities were generally estimated from the adjusted odds ratios from the biological derived logistic regression models. They were quoted as percentages in the results to avoid confusion with probability values derived from statistical significance testing.

(iv) Univariate and multilevel modelling of the semen parameter data - In addition to the approach using the binary division (into cases and controls), the hypotheses were also investigated by a direct examination of the continuous variables representing the results of the semen analysis for each of the occupational exposures of interest. Firstly, the data were examined in a univariate fashion using the descriptive statistics the mean, standard deviation, median and range. Given the degree of skewness observed, particularly for sperm concentration, the median was used as the comparator in most instances. When two samples were available for a particular individual the mean of the two samples was used in this analysis as the observation for that individual. Secondly, multilevel modelling [Goldstein, 1987] was used to calculate the difference in the semen parameter of interest (sperm concentration, motility or deformity) by exposure category (*eg* leatherworker or not leatherworker) having adjusted for the effects of other factors of interest. The other factors adjusted for were those that appeared as terms in most of the statistically derived multiple logistic regression models. These were operations (Yes:No) (appendix D), social class (III versus the rest) and Leicestershire resident status (Yes:No). For the analysis of the sperm concentration data a $\log_e (+1)$ transformation was used to normalise the data because of the skewed nature of these data. The motility and morphology data were near normal and did not require transformation prior to analysis. The level 1 residuals were checked and found to be approximately normally distributed for all three parameters. Intraclass

correlations were also calculated for the three semen parameters of interest.

The multilevel modelling provided an appropriate method of dealing with the fact that some of the men had two semen samples and some only had one available. This approach was valid because subjects (and their doctors) would be unlikely to know the first test results at the point at which they provided or failed to provide the second sample. As a consequence these data can be viewed as being missing at random. Dealing with the data in a continuous rather than binary fashion also increased the power of the analysis.

3.10 NON-PARTICIPANTS

Basic details about couples who declined to participate in the study were collected by review of the medical records. Semen analysis results were noted alongside these details. The collection of these data allowed an assessment of the impact of non-response upon the results.

3.11 PERMISSIONS, APPROVALS AND FUNDING

Approval for the study from the Leicestershire District Health Authority Ethics Committee was sought and granted in June 1988. Approval from the Ethics Committee of Kettering District Hospital was sought and granted in July 1990. The Leicestershire Division of Obstetrics and Gynaecology gave their support to the proposal in June 1988. All Obstetric and Gynaecology Consultants in Leicestershire allowed their patients to be approached and invited to participate in the study.

This study was primarily funded by the Health and Safety Executive (UK). A Wellcome Trust Research Training Fellowship funded JJK from September 1988 to April 1991.

RESULTS

4.1 THE RESPONSE

There were 2,184 women and 2,154 men, that is 2,154 couples and 30 women without partners, who were eligible for inclusion in the study and invited to participate. Of the 2,154 men 1,906 were interviewed, giving a response of 88.5%. Of the 2,184 women 2,123 were interviewed, a response of 97.2%. The respondents comprised 1,899 couples, seven men whose wives/partners were not interviewed and 224 women whose husbands/partners were similarly not interviewed. Table 4.1.1 gives the details of the response to the study.

Table 4.1.1: The response to the study

	Men	Women
Number eligible for inclusion	2,154	2,184
Number who refused to participate	248	61
Number interviewed	1,906	2,123
Response proportion	88.5%	97.2%

There were a further 26 couples, one woman and one man who were eligible for inclusion in the study having presented during the study period. However, these potential study participants had not been approached for an interview when interviewing ceased on the 27th November 1992, they are therefore not included in the response figures given in table

4.1.1. Five of the couples, the woman and the man were Leicester Royal Infirmary patients, six of the couples were Leicester General Hospital patients and 15 were Kettering General Hospital patients.

Of those women interviewed, 82.0% were interviewed in clinic, whereas of the men interviewed only 56.0% were interviewed in clinic; the remaining men and women were interviewed in their own homes. Seventeen (0.9%) men were interviewed through an interpreter, the remaining 1,889 (99.1%) were interviewed in English directly by one of the study interviewers. In comparison, 44 (2.1%) women were interviewed through an interpreter.

4.2 THE RELIABILITY OF THE DATA COLLECTION AND CODING

4.2.1 Reliability of the data collection

Fifteen men and women, approached at random, agreed to be re-interviewed. They were re-interviewed between one and four months (mean 2.5 months, median 2 months) after their original interview. The re-interviews were conducted by the same interviewer in 11 cases and by a different interviewer in the remaining four.

The range of individual items of information asked in each interview varied from 79 to 163 (mean 115, median 112). This variation was mainly due to the number of long term jobs (*ie* jobs in excess of six months duration) each interviewee reported having had. The number of answers to individual items of information which were not consistent between the original interview and the re-interview ranged from none to eight (mean 3.6, median 3.0). The mean proportion of inconsistent items was 3.1% (range 0% to 5.5%). For those interviewed by the same interviewer on both occasions the mean proportion of

inconsistent items was 2.8% (range 0% to 5.5%) compared to 3.8% (range 1.5% to 5.3%) for those interviewed by different interviewers. In general the interviewees tended to recall slightly more detailed information at re-interview and this accounted for the majority of the inconsistencies.

4.2.2 Reliability of the coding of social class and socio-economic group

An assessment of the reliability of the social class and socio-economic group (SEG) coding was performed on the coding of the current occupation using both the 1970 and 1980 editions of the OPCS Classification of Occupations [OPCS, 1970; OPCS, 1980]. Details of the current occupation from 60 questionnaires were blindly double coded. Table 4.2.1 shows the Kappa statistic and percentage agreement between the initial coding and the second blind coding for both occupational coding schedules.

Table 4.2.1: Kappa statistic and percentage of agreement for social class and socio-economic group(SEG) coding (n=60)

Category compared	1970 coding		1980 coding	
	Kappa statistic (95%CI)	Percentage agreement (95%CI)	Kappa statistic (95%CI)	Percentage agreement (95%CI)
Social class	0.85 (0.74, 0.95)	90.0% (79.5%,96.2%)	0.66 (0.53, 0.80)	83.3% (71.5%, 91.7%)
Socio-economic group	0.85 (0.75, 0.95)	88.3% (77.4%, 95.2%)	0.75 (0.63, 0.88)	83.3% (71.5%, 91.7%)

The Kappa statistics and the percentage agreements for the 1970 coding indicated that there was very good agreement between the first coding and the re-coding for both social class and SEG. The Kappa statistic and percentage agreement for the 1980 coding indicated that there was fair agreement for the social class coding and fair to good agreement for SEG.

For the coding using the 1970 classification, of the six cases where there was disagreement, equal numbers of cases were classified higher and lower on the social class scale on the second coding compared to the first. Whereas, for all seven cases with disagreement on the socio-economic coding the second coding placed all seven in lower socio-economic groups than did the first round of coding. In comparison, using the 1980 classification the distribution of the codes disagreeing were equally distributed between higher and lower for both social class and socio-economic group.

4.2.3 Reliability of the coding of specific occupations

The coding of two specific occupational groups, leatherwork and welding, was compared between the coding carried out using the 1970 and 1980 classification of occupation. There were 26 men whose occupations were coded as leatherworker by one or other of the two sets of coding. Table 4.2.2 gives the Kappa statistic and percentage agreement between the coding of the these 26 and the remaining 1880 men.

Table 4.2.2: Kappa statistic and percentage of agreement for the coding of leatherwork and welding (n=1906)

Category compared	1970 versus 1980 coding			
	Kappa statistic	95% confidence interval	Percentage agreement	95% confidence interval
Leatherwork	0.87	0.76, 0.97	99.7%	99.3%, 99.9%
Welding	0.93	0.84, 1.03	99.9%	96.6%, 100%

All 26 men had their occupation defined as a leatherworker by the coding using the 1970 classification, however, six of their occupation coded to more general categories by the coding using the 1980 classification. For example, one man described himself as a technical manager in a tannery and was coded as a technical manager using the 1980 classification. However, the description of his work included: office work, work in the leather spraying area and sampling area, and supervision of shopfloor work. Under the coding using the 1970 classification, by the nature of his potential exposures, this man was classified as a leatherworker. Given the differences in results following this comparison a decision was made to use the current occupation data as classified using the 1970 classification for all subsequent analyses of current occupation. The occupational histories of all 26 men defined as leatherworkers under the 1970 classification coding were reviewed and a decision was made to define them all as leatherworkers for the purposes of all subsequent analyses.

There were 16 men whose current occupation was coded as a welder by one or other of the classification (1970 or 1980). Of these 14 were classified as a welder by both sets of

coding and two were coded as a welder by one classification (1970) and not by the other (1980) and vice versa. The Kappa statistic and percentage agreement results are given in table 4.2.2. On review of the two histories where the coding did not agree, it was clear that both men were actually welders and as a consequence both were treated as such for all subsequent analyses.

4.2.4 Reliability of general occupation coding

The reliability of the coding of occupation in general was assessed by comparing the coding of the current occupation for 60 questionnaires which had been blindly double coded using both the 1970 and 1980 OPCS classifications of occupation. Table 4.2.3 shows the percentage agreement between the initial coding and the second blind coding, for the occupational coding, whether the occupation was classified as manual or non-manual and the industry code.

Table 4.2.3: Percentage of agreement for occupation, manual/non-manual and industry coding

Category compared	Percentage agreement	
	1970 n = 60	1980 n = 60
Occupation code	86.7%	91.7%
Manual/Non-manual	*	98.3%
Industry code	96.7%	*

* Not coded using this classification

As can be seen from table 4.2.3 the agreement for the occupational coding using the 1980 classification, for manual versus non-manual and the industry classification indicated a very high level of agreement. The percentage agreement of the occupational coding using the 1970 classification indicated a high level of agreement. The Kappa statistic for the classification of the occupation as manual or non-manual was 0.90 (95%CI 0.78, 1.01) which indicated there was very high overall agreement between the first and second coding. Differences in classification largely arose from including in the classification the grade of an occupation. For example, a laboratory technician working in a specific scientific area was coded as the specific: 02401 (1980 classification): Scientists, physicist, mathematicians. Whereas when the grade of work (laboratory technician) was taken into account the code was 03001: Laboratory technician. The was no evidence of a systematic variation of coding from the more general to the more specific, or vice versa, between the initial coding and the re-coding.

4.3 CHARACTERISTICS OF THE MALE RESPONDENTS

Although both male and female partners were interviewed in this study, for the purposes of this thesis and the primary hypothesis it addresses, only the results relating to the male respondents will be presented.

4.3.1 Demographic characteristics

The demographic characteristics of all 1,906 male respondents are given in table 4.3.1.

Table 4.3.1: Demographic characteristics of all male respondents (n = 1906)

Characteristics	Number	Percent
Age group:		
18 - 19 yrs	5	0.3%
20 - 24 yrs	167	8.8%
25 - 29 yrs	621	32.6%
30 - 34 yrs	619	32.5%
35 - 39 yrs	324	17.0%
40 - 44 yrs	110	5.8%
45 - 49 yrs	42	2.2%
50 - 54 yrs	10	0.5%
55 - 59 yrs	2	0.1%
60 + yrs	5	0.3%
Missing	1	0.1%
Marital status:		
Married	1590	83.4%
Living together	300	15.7%
Not living together	16	0.9%
Place of birth:		
United Kingdom	1520	79.7%
Africa	193	10.1%
India, Pakistan & Bangladesh	118	6.2%
Europe excluding the UK	32	1.7%
Americas & West Indies	15	0.8%
China & Australia	13	0.7%
Middle East	12	0.6%
Missing	3	0.2%
Current employment status:		
Working	1747	91.7%
Unemployed	143	7.5%
Student	12	0.6%
Retired	4	0.2%
Area of residence*:		
Leicestershire	1606	83.4%
Northamptonshire	259	13.6%
Elsewhere	41	2.2%

* Residence defined on the basis of postcode and address

Table 4.3.1 contd: Demographic characteristics of all male respondents (n = 1906)

Characteristics	Number	Percent
Social class (1980 classification):		
I	135	7.1%
II	435	22.8%
IIIN	193	10.1%
IIIM	758	39.8%
IV	322	16.9%
V	48	2.5%
Armed forces & students	12	0.6%
Never worked	3	0.2%
Socio-economic group (1980 classification):		
1. Employers in industry - large est*	119	6.2%
2. Employers in industry - small est*	187	9.8%
3. Self-employed professionals	12	0.6%
4. Professional employees	120	6.3%
5. Ancillary workers, artists, non-manual supervisors	184	9.7%
6. Junior non-manual workers	149	7.8%
7. Personal service workers	22	1.2%
8. Manual foremen and supervisors	87	4.6%
9. Skilled manual workers	530	27.8%
10. Semi-skilled manual workers	283	14.8%
11. Unskilled manual workers	46	2.4%
12. Own account workers	139	7.3%
13. Farmers - employers & managers	4	0.2%
14. Farmers - own account	1	0.1%
15. Agricultural workers	9	0.5%
16. Armed forces	10	0.5%
17. Inadequately described	0	--
18. Students who had never worked	2	0.8%
19. Never worked	3	0.2%

* Establishment

The men in the study ranged in age from 18 to 65 years (mean 31.4 years) and

approximately two thirds of them were aged 25 to 34 years. As can be seen from table 4.3.1, the majority of the men were married and 99.1% were either married or living with their partner. Nearly 80% of the men were born in the United Kingdom and a further 16% were born in either the Indian subcontinent or Africa. Over 90% of the men were employed with only 7.5% unemployed. The vast majority (84.3%) of the men were Leicestershire residents, 13.6% were Northamptonshire residents and the remaining 2.2% lived in neither of these counties. Social class was defined on the basis of the current or most recent occupation for those unemployed. Half of the respondents were classified to social class III, namely skilled non-manual (IIIN) and skilled manual (IIIM). The majority of those not classified to III were classified to I and II; these two categories combined represented just over a quarter of all the respondents. Over 40% of the men were classified to socio-economic groups (SEG) nine and ten.

The demographic characteristics of the 1,606 male respondents who were Leicestershire residents, as defined by their postcode and address are given in table 4.3.2. For comparative purposes the age distribution, marital status and current employment status of the Leicestershire male population aged 20-44 years, derived from the 1991 census [OPCS, 1992a; OPCS, 1992b], are also given in the table. The census data relating to the age group 20-44 years was chosen for comparison as 96.4% of the Leicestershire resident male respondents were aged 20-44 years. However, for place of birth, social class and socio-economic group, the published census tabulations were not given by age group. Thus, the census data given in the table relates to all males for country of birth and all males aged 16 years or greater for social class and socio-economic group.

Table 4.3.2: Demographic characteristics of Leicestershire resident male respondents (n = 1606) and the Leicestershire male population derived from the 1991 census [OPCS, 1992a; OPCS, 1992b]

Demographic characteristics	Male respondents n	Male respondents %	Leicestershire population %
Age: Range	18-65 yrs		20-44 yrs†
Mean	31.6 yrs*		31.9 yrs
Marital status†:			
Married	1361	84.7%	56.7%
Living together	235	14.6%	#
Not living together	10	0.7%	#
Place of birth‡:			
United Kingdom	1239	77.1%	90.9%
Africa	188	11.7%	2.8%
India, Pakistan & Bangladesh	114	7.1%	3.1%
Rest of Europe	28	1.7%	1.7%
Middle East	12	0.7%	0.1%
China & Australia	12	0.7%	0.1%
Americas & West Indies	10	0.6%	0.4%
Rest of world	0	--	0.9%
Missing	3	0.2%	--
Current employment status†:			
Working	1471	91.6%	85.6%
Unemployed	120	7.5%	8.3%
Student	11	0.7%	3.3%
Retired	4	0.2%	0.1%
Other	0	--	2.7%

* The mean age of those men 20-44 yrs was 30.9 years
† For the census data the 20-44 yrs age group was selected for comparative purposes as being the most appropriate group to compare the infertility presenters with
# Unable to determine this figure from published tabulations
‡ The census information by place of birth given in the table relates to males of all ages as country of birth by age group was not available from published census tabulations
-- Not applicable

Table 4.3.2 contd: Demographic characteristics of Leicestershire resident male respondents (n = 1606) and the Leicestershire male population derived from the 1991 census [OPCS, 1992a; OPCS, 1992b]

Demographic characteristics	Male respondents n	Male respondents %	Leicestershire population %
Social class* (1980 classification):			
I	114	7.1%	6.5%
II	360	22.4%	26.5%
IIIN	168	10.5%	10.0%
IIIM	645	40.2%	34.1%
IV	272	16.9%	15.7%
V	33	2.1%	4.5%
Armed forces & students	11	0.7%	0.7%
Never worked	3	0.2%	1.0%
Missing	--	--	1.2%
Socio-economic group* (1980 classification):			
1. Employers in industry - large est	85	5.3%	5.5%
2. Employers in industry - small est	164	10.2%	13.1%
3. Self-employed professionals	9	0.6%	1.1%
4. Professional employees	103	6.4%	5.4%
5. Ancillary workers, artists, non-manual supervisors	161	10.0%	8.2%
6. Junior non-manual workers	128	8.0%	8.4%
7. Personal service workers	20	1.2%	1.0%
8. Manual foremen and supervisors	65	4.0%	3.0%
9. Skilled manual workers	462	28.8%	24.0%
10. Semi-skilled manual workers	234	14.6%	12.8%
11. Unskilled manual workers	33	2.1%	3.9%
12. Own account workers	116	7.2%	8.8%
13. Farmers - employers & managers	3	0.2%	0.5%
14. Farmers - own account	0	--	0.6%
15. Agricultural workers	9	0.6%	0.7%
16. Armed forces	10	0.6%	0.9%
17. Inadequately described	0	--	1.2%
18. Students who had never worked	1	0.1%}	}1.0%
19. Never worked	3	0.2%}	

* The census information for social class and socio-economic group given in the table relates to males aged 16 years and older as social class and socio-economic group by age group were not available from published census tabulations

As can be seen from table 4.3.2 there were some differences between the male Leicestershire respondents and the general male population of Leicestershire. The respondents had a similar age distribution within the range 20-44 years. However, compared to the general population a much greater proportion of the respondents were married and a slightly greater proportion were currently working. The distribution of country of birth was markedly different. Fewer of the respondents had been born in the United Kingdom and a greater proportion had been born in Africa or the Indian sub-continent. Since the migrant population in Leicestershire is weighted towards the younger ages [OPCS, 1992a] it was impossible to tell how much of this difference between the two groups was explained by the fact that the general population comparator data included males of all ages rather than only those men aged 20 to 44 years. The social class and socio-economic group distributions of the respondents was very similar to the general population aged 16 years and over.

4.3.2 Infertility history

The history of infertility of the male respondents is given below in table 4.3.3. The type of male infertility was defined on the basis of the male partner's history alone. Primary male infertility was defined as never having fathered a pregnancy and secondary male infertility was defined as having fathered a pregnancy with their current or any past partner regardless of the pregnancy outcome.

Table 4.3.3: Infertility history of all male respondents (n=1906)

Characteristics	Number	Percent
Male infertility type:		
Primary	1003	52.6%
Secondary	894	46.9%
Not known	9	0.5%
Duration of time trying to conceive:		
Less than 12 months	140	7.3%
12 - 23 months	540	28.3%
24 - 35 months	493	25.9%
36 months or longer	722	37.9%
Missing	11	0.6%
Duration of time living together:		
Less than 12 months	34	1.8%
12 - 23 months	114	6.0%
24 - 35 months	233	12.2%
36 months or longer	1524	80.0%
Missing	1	0.1%

As can be seen from table 4.3.3, over half of the respondents had never fathered a pregnancy. Of the remaining 894 men 45.7% had fathered a child with their current partner; 25.1% had fathered a pregnancy with their current partner which had not resulted in a child; and 29.2% had fathered a pregnancy with a previous partner, although it was not known whether a child resulted from these pregnancies as information about these particular pregnancy outcomes was not sought in the interview.

Of all male respondents, 92.1% reported having tried to conceive for 12 months or more before presentation and interview. Over a third had been trying for three years or more. The interviewees were also asked how long they and their partner had been living

together. This was asked in preference to the duration of marriage in an attempt to elicit more accurate information about the likely duration of a sexual relationship but without asking the question directly. Thirty-four (1.8%) of the men reported that they and their partner had been living together for less than 12 months. Eighteen percent had been together for between one and three years and 80% had been together for three years or longer. Of the men who said they had been living with their partner for less than 12 months, 44.1% were married; of those together for 12-23 months 64.0% were married; of those together 24-35 months 68.7% were married; and of those together 36 or more months, 88.0% were married.

The results of the responses to the infertility questions from both the male and female partners were combined for the 1,899 couples for whom an interview with both partners had been carried out. For 78.1% of couples, both partners agreed as to the duration of time they had been trying to conceive when that duration of time was grouped as: less than 12 months, 12-23 months, 24-35 months and 36+ months. For 11.5% of couples the female partner reported a longer duration of attempted conception than the male partner and in 10.4% of couples this was reversed. Of the 416 couples where there was disagreement, 257 of the couples (62.0% of 416) disagreed by 12 months or more and 140 (33.7% of 416) disagreed by six to 12 months. A 'couple duration of trying to conceive' variable was created by combining the responses of the two partners in each couple. For those couples where the partners were not in agreement about the duration of trying, the longer of the two estimates of duration of time was taken for the measure of the couple duration of trying to conceive. These results are given in table 4.3.4.

Each partner was also asked how long they had been living with their partner, 92% of

couples agreed as to this duration when the duration was grouped as: less than 12 months, 12-23 months, 24-35 months and 36+ months. In 4.2% of couples the female partner reported living together longer than the male partner and vice versa in 3.7% of couples. A variable 'couple duration of living together' was similarly created. The results are given in table 4.3.4.

Table 4.3.4: Combined infertility history of the 1,899 couples interviewed

Characteristics	Number	Percent
Couple infertility type:		
Both primary	857	45.1%
Female primary male secondary	184	9.7%
Male primary female secondary	142	7.5%
Both secondary	703	37.3%
Not known	8	0.4%
Couple duration of time trying to conceive:		
Less than 12 months	85	4.5%
12 - 23 months	471	24.8%
24 - 35 months	507	26.7%
36 months or longer	833	43.9%
Missing	3	0.2%
Couple duration of time living together:		
Less than 12 months	20	1.1%
12 - 23 months	95	5.0%
24 - 35 months	205	10.8%
36 months or longer	1578	83.1%
Missing	1	0.1%

As can be seen from table 4.3.4, 85 (4.5%) couples had presented after trying to conceive for less than 12 months. Of these 39 (2.1% of 1,899) had primary couple infertility; ten (0.5% of 1,899) had primary female and secondary male infertility; four (0.2% of 1,899)

had primary male and secondary female infertility; and 32 (1.7% of 1,899) had couple secondary infertility.

Fifteen of the 39 with couple primary infertility had presented having only been trying to conceive for six months or less. In four of the 39 couples (10%) the male partner had oligozoospermia, 15% had one normal sperm count and one oligozoospermic count, 49% had one or more normal sperm counts and 26% did not have a semen analysis result available. Of the 46 couples who had secondary infertility affecting one or both of the partners and who presented with infertility of less than 12 months duration, 6.5% had oligozoospermia; 54.4% did not have oligozoospermia; and 39.1% did not have a semen analysis result available. Thus, oligozoospermia alone does not appear to explain the early presentation for specialist investigation for the majority of these early presenters.

4.3.3 Occupational characteristics and exposures

The details of the current occupational status of all 1906 men interviewed are given in table 4.3.5.

Table 4.3.5: Current occupational histories of all male respondents (n=1906)

Occupational characteristics	Number	Percent
Current occupational status:		
Working*	1747	91.7%
Unemployed -		
worked in the past	140	7.3%
never worked	3	0.2%
Student -		
worked in the past	11	0.6%
never worked	1	0.1%
Retired -		
worked in the past	4	0.2%
Number of current jobs:		
One job	1723	90.4%
Two jobs	24	1.3%
Not currently working	159	8.3%

* Included one man who was disabled who currently worked at home

Of the 143 men unemployed when interviewed three (2.1%) had never worked; 100 (69.9%) had worked in the previous 12 months; 24 (16.8%) had worked 13-24 months previously; 6 (4.2%) had worked over two but less than three years previously; 9 (6.3%) had not worked for three or more years, with one of these men not having worked for 12 years; and this information was missing for one man.

Of the 12 men who were students when interviewed, one had never worked; four had worked in the previous 12 months; three had worked over 12 months previously; three had not worked for four years; and this information was missing for one student. All four of the men who were retired when interviewed had worked in the past. One had worked 12

months previously, one had worked 13 months previously, one had last worked over three years previously and one had not worked for 15 years.

The details of current exposure to specific occupational exposures for those men currently working and the most recent occupational exposures for those not currently working are given in table 4.3.6.

Table 4.3.6: Specific occupational exposures by current occupational status for those men who had ever worked (n=1902*)

Exposure	Working (n = 1747)		Not working† (n = 155)	
	Number	Percent	Number	Percent
Manual versus non-manual job:				
Manual	996	57.0%	119	76.2%
Non-manual	742	42.5%	36	23.2%
Not applicable‡	9	0.5%	0	--
Work rota:				
Days	1392	79.7%	134	86.5%
Day shifts	104	6.0%	4	2.6%
Nights	36	2.1%	4	2.6%
Night shifts	8	0.5%	2	1.3%
Rotating shifts	147	8.4%	5	3.2%
Evenings	18	1.0%	1	0.6%
Days and nights	9	0.5%	0	--
Other	31	1.8%	5	3.2%
Missing	2	0.1%	0	--
Place of work:				
One place	1117	63.9%	100	64.5%
Travelling	466	26.7%	46	29.7%
Variable	162	9.3%	8	5.2%
Missing	2	0.1%	1	0.6%
Job cleanliness:				
Clean	1046	59.9%	79	51.0%
Dirty	466	26.7%	55	35.5%
Very dirty	100	5.7%	8	5.2%
Variable	133	7.6%	13	8.4%
Missing	2	0.1%	0	--

* Four men, including one student had never worked
† Includes unemployed, students and retired men who have worked in the past
‡ Work in the armed forces is not classified by manual or non-manual status

Table 4.3.6 contd: Specific occupational exposures by current occupational status for those men who have ever worked (n=1902*)

Exposure	Working (n = 1747)		Not working† (n = 155)	
	Number	Percent	Number	Percent
Job temperature:				
Cold	65	3.7%	14	9.0%
Warm	850	48.7%	65	41.9%
Hot	149	8.5%	15	9.7%
Very hot	44	2.5%	5	3.2%
Variable	638	36.5%	56	36.1%
Missing	1	0.1%	0	--
Job noise:				
Quiet	366	21.0%	30	19.4%
Background noise	617	35.3%	52	33.5%
Noisy	447	25.6%	45	29.0%
Very noisy	137	7.8%	13	8.4%
Variable	179	10.2%	15	9.7%
Missing	1	0.1%	0	--
Solvent use:				
Yes	557	31.9%	32	20.6%
No	1187	67.9%	123	79.4%
Missing	3	0.2%	0	--
Glue use:				
Yes	401	23.0%	21	13.5%
No	1345	77.0%	134	86.5%
Missing	1	0.1%	0	--
Cleaning agents:				
Yes	423	24.2%	38	24.5%
No	1322	75.7%	117	75.5%
Missing	2	0.1%	0	--

* Four men, including one student had never worked
† Includes unemployed, students and retired men who have worked in the past

Table 4.3.6 contd: Specific occupational exposures by current occupational status for those men who have ever worked (n=1902*)

Exposure	Working (n = 1747)		Not working† (n = 155)	
	Number	Percent	Number	Percent
Paint spraying:				
Yes	131	7.5%	10	6.5%
No	1615	92.4%	145	93.5%
Missing	1	0.1%	0	--
Colour mixing solutions:				
Yes	45	2.6%	6	3.9%
No	1701	97.4%	149	96.1%
Missing	1	0.1%	0	--
Other chemical use:				
Yes	703	40.2%	60	38.7%
No	1042	59.6%	95	61.3%
Missing	2	0.2%	0	--
Photocopier use:				
Yes	727	41.6%	24	15.5%
No	1019	58.3%	131	84.5%
Missing	1	0.1%	0	--
VDU‡ use:				
Yes	583	33.4%	14	9.0%
No	1163	66.6%	131	91.0%
Missing	1	0.1%	0	--
Microwave use:				
Yes	150	8.6%	4	2.6%
No	1596	91.4%	151	97.4%
Missing	1	0.1%	0	--

* Four men, including one student had never worked
† Includes unemployed, students and retired men who have worked in the past
‡ Computer visual display unit

Table 4.3.6 contd: Specific occupational exposures by current occupational status for those men who have ever worked (n=1902*)

Exposure	Working (n = 1747)		Not working† (n = 155)	
	Number	Percent	Number	Percent
Ultrasound equipment use:				
Yes	39	2.2%	2	1.3%
No	1707	97.7%	153	98.7%
Missing	1	0.1%	0	--
Radiation exposure:				
No	1515	86.7%	146	94.2%
X-rays	21	1.2%	1	0.6%
Isotopes	23	1.3%	0	--
UV exposure	154	8.8%	7	4.5%
Multiple	12	0.7%	1	0.6%
Other	14	0.8%	0	--
Missing	8	0.5%	0	--
Welding‡:				
Yes	161	9.2%	9	5.8%
No	1582	90.6%	146	94.2%
Missing	4	0.2%	0	--

* Four men, including one student had never worked
† Includes unemployed, students and retired men who have worked in the past
‡ These men were not necessarily all welders but they performed welding as part of their job

There was little variation in specific occupational exposures between those men currently working and those who were not currently working. The main differences were that those men not currently employed were more likely to have had a manual occupation than those currently working (76.2% versus 57.0% respectively). They were less likely to have had exposure to solvents (20.6% versus 31.9% respectively), exposure to glue (13.5% versus

23.0%), to have used a photocopier (15.5% versus 41.6%), and to have used a computer visual display unit (VDU) (9.0% versus 33.4%).

4.3.4 Specific exposures in the context of hobbies

The details of contact with specific exposures of interest in the context of hobbies or other activities at home are given in table 4.3.7. As can be seen from this table, the only common specific exposure of interest used at home was a microwave and 'other chemicals'. The 'other chemicals' group consisted of a very wide variety of substances mentioned by the respondents, for example, common household cleaning agents.

Table 4.3.7: Contact with specific exposures in the context of hobbies (n=1906)

Hobby exposure	Number	Percent
Solvent use:		
Yes	178	9.3%
No	1728	90.7%
Glue use:		
Yes	153	8.0%
No	1753	92.0%
Cleaning agent use:		
Yes	90	4.7%
No	1815	95.2%
Missing	1	0.1%
Paint solutions:		
Yes	99	5.2%
No	1806	94.8%
Missing	1	0.1%
Colour mixing solutions:		
Yes	6	0.3%
No	1899	99.6%
Missing	1	0.1%
Other chemicals:		
Yes	325	17.1%
No	1580	82.9%
Missing	1	0.1%
Welding:		
Yes	157	8.2%
No	1746	91.6%
Missing	3	0.2%
Microwave use at home:		
Yes	1258	66.0%
No	647	33.9%
Missing	1	0.1%

4.3.5 Medical history

Medical history details were collected and are given in table 4.3.8. The details of all medical conditions and operations reported were reclassified by reference to the Oxford Textbook of Medicine and a specialist infertility textbook [OTM, 1996; Lipshultz & Howards, 1991] into conditions which may or may not potentially impair male fertility, either by virtue of the pathogenesis of the disease or its treatment. The list of medical conditions and operations defined as potentially affecting male fertility are given in appendix D. Information about current and past medication use was also collected. Current medications included both prescription and over the counter drugs. All medications were classified, by reference to the British National Formulary [BNF, 1992], into those which may potentially impair male fertility and those which are unlikely to do so. The list of drugs defined as potentially affecting male fertility, together with their possible effects, is given in appendix D.

As can be seen from table 4.3.8, whilst a fifth of men had had a serious medical condition in the past, on the basis of the definitions used in the study, less than 2% had had a condition which may potentially have affected their fertility. Over 40% of men reported having had mumps. However, only two spontaneously said they had had orchitis. The question about orchitis was not specifically asked, but would probably have been of more relevance than the question about mumps. Nearly half the men had had an operation, although less than 10% had had an operation which might have directly affected their fertility. Just over one fifth of men had had pelvic or abdominal x-rays at some stage in their life. Only 2.9% were currently taking medications which might have affected their fertility and 4.2% had taken medications in the past which may have potentially affected their fertility. However, only one of the drugs, cyclophosphamide, reported to have ever

been taken by any of the men is known to cause sterility. This drug had been taken in the past by one respondent although the indications for its use was not reported. This man did indeed have azoospermia.

Table 4.3.8: Medical history details (n=1906)

Medical history	Number	Percent
History of serious medical condition:		
Yes	387	20.3%
No	1516	79.5%
Missing	3	0.2%
Ever had a medical condition which may potentially impair fertility*:		
Yes	34	1.8%
No	1872	98.2%
Ever had mumps:		
Yes	801	42.0%
No	734	38.5%
Don't know	359	18.8%
Missing	12	0.6%
Ever had an operation of any type:		
Yes	901	47.3%
No	1002	52.6%
Missing	3	0.2%
Ever had an operation which may potentially impair fertility*:		
Yes	164	8.6%
No	1742	91.4%
Ever had an x-ray:		
Yes of pelvis and abdomen	406	21.3%
Yes not of pelvis or abdomen	1361	71.4%
No	139	7.3%
Currently† taking a medication which may potentially impair fertility*:		
Yes	55	2.9%
No	1851	97.1%
Ever taken a medication in the past which may potentially impair fertility*:		
Yes	80	4.2%
No	1826	95.8%

* See appendix D for the lists of those defined as potentially impairing fertility
† Includes prescription and over the counter drugs

4.3.6 Lifestyle exposures

Questions were asked about three specific aspects of lifestyle which may affect fertility, namely cigarette smoking, alcohol consumption and the consumption of coffee or cola containing caffeine. In retrospect is was somewhat of an oversight to have omitted questions about caffeinated tea. Thus whilst the quantities of caffeinated coffee and cola were collected, a history of total caffeine intake was not. For this reason coffee and cola consumption was combined into a single binary (Yes/No) variable (table 4.3.9). Estimates of cigarette smoking and alcohol consumption are given in table 4.3.9 together with population data for men aged 20-49 years derived from the General Household Survey 1992 [Thomas *et al*, 1994].

Comparison between the study respondents and the General Household Survey (GHS) results indicated that the proportion of men who had never smoked was similar in both groups. However, of the ever smokers, a greater proportion of the study population were current rather than ex-smokers compared to the GHS data. In contrast the alcohol consumption of the study population was skewed towards the abstainer/low (>0 to 4 standard drinks per day) end of the range compared to the GHS data. The Leicestershire population has a relatively unusual racial and religious mix compared to the general population and the possibility that this might have explained the differences in alcohol consumption and tobacco use was explored by excluding those men from the study population whose place of birth was given as Africa, India, Pakistan, China and the Middle East. The alcohol consumption pattern of the remaining 1,570 men was remarkably similar to that in the GHS population. However, the difference in the cigarette consumption pattern was exaggerated further by this restriction on place of birth.

Table 4.3.9: Lifestyle exposures to cigarettes, alcohol and coffee and cola consumption compared with General Household Survey (GHS) data (n=1906)

Lifestyle exposures	Number	Percent	GHS*(%)
Cigarette smoking:			
Never	779	40.9%	45%
Ex-smoker for more than two years	240	12.6%	21%†
Ex-smoker for two years or less	98	5.1%	
Current 1-14 cigarettes per day	354	18.6%	34%†
Current 15-24 cigarettes per day	346	18.2%	
Current 25+ cigarettes per day	89	4.7%	
Alcohol consumption‡:			
Abstainer	233	12.2%	4%
>0 - 4 standard drinks per day	1306	68.5%	73%
>4 - 6 standard drinks per day	211	11.1%	12%
> 6 standard drinks per day	134	7.0%	12%
Drinker: but volume per day missing	22	1.2%	#
Caffeinated coffee or cola consumption:			
Yes	1709	89.7%	#
No	197	10.3%	#

* General Household survey data for 1992 [Thomas *et al*, 1994]
† The GHS data reported the total ex-smoker data without division into when the smoker had quit, similarly the GHS data do not allow division into the current smoking categories used for the infertility presenters
‡ A standard drink contains 10g of alcohol
# Not available from this source

The comparison of cigarette and alcohol data with the GHS data suggested that the presence of male infertility had little impact upon these habits.

4.4 COMPARISONS WITH THE LEICESTERSHIRE PERINATAL MORTALITY CONTROLS - SET I OF THE CASE CONTROL ANALYSES

This set of case control analyses were designed to test the hypotheses that leatherwork and work with solvents (occupations so defined *a priori* from job title, see methods section 3.9.3 and appendix C) are associated with an increased risk of presenting for the investigation of infertility. Leatherwork was defined two ways for this purpose, firstly as leatherworkers and secondly as work in the leather industry (see appendix C for the job titles for these two groups).

4.4.1 Comparisons with PNMS controls: Definition of cases

The cases for these comparisons were defined as all 1606 Leicestershire residents in the infertility study population. Only Leicestershire residents were included as the control population was derived from Leicestershire residents.

4.4.2 Comparisons with PNMS controls: Definition of controls

The control group for these comparisons was obtained from the control population of the Leicestershire Perinatal Mortality Survey (PNMS). Those controls with a history of infertility were excluded from the group used in these analyses. The control group thus comprised the 1013 PNMS control fathers who did not have a history of infertility and whose baby was born in 1985 to 1992 inclusive.

4.4.3 Comparisons with PNMS controls: Leatherwork

Table 4.4.1 gives the results of the case control comparison for exposure to leatherwork in the current or, for those currently unemployed, their most recent job.

Table 4.4.1: Case control comparison for exposure to leatherwork, comparing infertility presenters as the cases to PNMS controls. Leicestershire residents only.

	Leatherwork (current or most recent)		
	Yes	No	Total
Cases = infertility presenters	14	1592	1606
Controls = PNMS controls	8	1005	1013
Total	22	2597	2619

Odds ratio = 1.10; 95%CI 0.46, 2.63

The odds ratio for this comparison was 1.10. This indicates that the infertility presenters were 1.1 times more likely to be leatherworkers (currently or in their most recent occupation) than were the controls. This result suggests that leatherwork is associated with only a 10% excess risk of leading to presentation for the investigation of infertility. The result was not statistically significant and indeed this finding, as indicated by the 95% confidence interval, is compatible with over a 50% reduction in risk and a 160% increase in risk.

4.4.4 Comparisons with PNMS controls: Work with solvents

Table 4.4.2 shows the findings when exposure to work involving solvents, as defined on the basis of job title (see methods 3.9.3 and appendix C), was compared between cases and controls.

Table 4.4.2: Case control comparison for exposure to work involving solvents, comparing infertility presenters as the cases to PNMS controls. Leicestershire residents only.

	Solvent work (current or most recent)		
	Yes	No	Total
Cases = infertility presenters	148	1458	1606
Controls = PNMS controls	56	957	1013
Total	204	2415	2619

Odds ratio = 1.73; 95%CI 1.26, 2.38

As can be seen the odds ratio for this comparison was 1.73 indicating that infertility presenters were 1.7 times more likely to have a current or most recent job which involved work with solvents compared to the controls. This suggests that work with solvents is associated with a 70% excess risk of leading to presentation for the investigation of infertility. The 95% confidence interval indicates that this result was statistically significant and is therefore unlikely to be due to chance alone.

4.4.5 Comparisons with PNMS controls: Work in the leather industry

The results of the case control comparison for work in the leather industry (current or most recent job) is given in table 4.4.3.

Table 4.4.3: Case control comparison for exposure to work in the leather industry, comparing infertility presenters as the cases to PNMS controls. Leicestershire residents only

	Leather industry (current or most recent)		
	Yes	No	Total
Cases = infertility presenters	32	1574	1606
Controls = PNMS controls	23	990	1013
Total	55	2564	2619

Odds ratio = 0.88; 95%CI 0.51, 1.51

The odds ratio for this comparison was 0.88. This indicates that infertility presenters were 20% less likely to work in the leather industry than the controls. This suggests that work in the leather industry was associated with a slightly decreased risk of presenting with infertility, although this result was not statistically significant.

4.4.6 Comparisons with PNMS controls: Effect of redefining the control group

For the three case control comparisons given above, the control group comprised fathers of the PNMS controls where a history of infertility had not been reported. Given that in the PNMS such a history was derived from the medical notes, rather than on direct questioning, it was possible that the medical notes would not necessarily reflect a true history and that there may have been differential reporting to the medical practitioner (and thus the PNMS control data collection) of an infertility history. For this reason the three case control comparisons were repeated using all the PNMS controls regardless of infertility history. Table 4.4.4 gives a comparison of the two sets of results.

Table 4.4.4: Comparison of results for current and most recent employment using two methods for the definition of the PNMS controls

Comparisons	Controls excluding those with infertility history reported		All controls regardless of infertility history	
	OR	95%CI	OR	95%CI
Leatherwork	1.10	0.46, 2.63	1.01	0.44, 2.34
Solvent work	1.73	1.26, 2.38	1.72	1.26, 2.35
Leather industry	0.88	0.51,1.51	0.86	0.50, 1.47

As can be seen from the results in table 4.4.4 including all the PNMS controls as compared to only including those without a reported history of infertility had very little impact upon the results and thus the inferences drawn. The greatest change was in the comparison for leatherwork where excluding those controls with a history of infertility increased the odds ratio from 1.01 (all controls) to 1.10 (excluding the infertile group). However, the inferences from both these results are similar.

4.5 SEMEN ANALYSIS RESULTS OVERALL

Of the 1,906 men interviewed in the study only 1,586 (83.2%) had at least one semen sample result available. Of the 1,586 men, 934 (58.9%) had two or more results available of which the earliest two were always taken for inclusion in the study analysis.

4.5.1 Semen intraclass correlation results

The intraclass correlation is an estimate of the proportion of all variation that is explained by real differences between individuals. The intraclass correlation for sperm concentration was 0.70 indicating a strong correlation. The results for sperm motility was 0.57, indicating a good correlation and for morphology was 0.41 indicating a moderate correlation. These three results indicated that in all three parameters there was a substantial amount of real variation to be investigated in an aetiological study.

4.5.2 Comparisons between Leicestershire residents and the rest

The semen analysis results were divided into those relating to Leicestershire residents and those to non-Leicestershire residents. Whilst there would have been some misclassification this division would have broadly divided the samples into those analysed in Leicestershire in the Leicester Royal Infirmary microbiology department and those not analysed there. Table 4.5.1 gives the characteristics of the semen sample results by Leicestershire resident status. For those men with two samples the means of the sample parameters were used as the result for each of these men. For those men with only one result that single result was used. The results for each of the semen parameters, sperm concentration, motility and deformity were divided into binary groups on the basis of the WHO criteria [1987]. The sperm concentration was divided into whether oligozoospermia present or not (Yes:No). Oligozoospermia was defined as being present when the sperm

concentration was 20 x10^6 per ml or less in all samples tested for each man. Low motility was defined as having 50% or less motile sperm present in all samples tested. High deformity was defined as having 70% or greater deformed sperm in all samples tested.

Table 4.5.1: Semen sample characteristics for Leicestershire and non-Leicestershire residents (n=1586)

Semen parameters	Leicestershire resident	Non-Leicestershire resident
Sperm concentration (x 10^6 per ml)		
Number of men †	1346	240
Mean	62.3	65.1
St Dev	66.2	46.8
Median	45.0	61.0
Range	0 - 565	0 - 280
% with oligozoospermia*	24.9%	14.2%
Sperm motility (%)		
Number of men †	1343	240
Mean	47.4	54.6
St Dev	22.1	21.9
Median	50.0	60.0
Range	0 - 95	0 - 91
% with low motility*	47.4%	29.3%
Sperm deformity (%)		
Number of men †	1333	232
Mean	40.5	28.4
St Dev	20.1	20.4
Median	40.0	21.3
Range	0 - 98	0 - 95
% with high deformity*	7.0%	6.5%

† The number of men changed between the different parameters as not all parameters were assayed in each sample for each man

* Binary terms based on the World Health Organisation classification [WHO, 1987]

As can be seen from table 4.5.1 there were considerable differences in all three semen parameters between Leicestershire and non-Leicestershire residents. The Leicestershire residents had a lower median sperm concentration, a lower median motility and a higher median deformity. These differences were reflected in the binary terms in a higher proportion with oligozoospermia, a higher proportion with low motility and a higher proportion with high deformity. It seemed most likely that these differences were due to differences in semen analysis between pathology centres rather than being true differences. For this reason a binary variable defining place of residence (Leicestershire residence: Yes/No) was included as a term to take this effect into account in all subsequent mathematical models.

4.6 WITHIN INFERTILITY PRESENTER ANALYSIS AND DEFINITIONS OF SET II OF THE CASES AND CONTROLS: LEATHERWORK

The second set (set II) of the case control analyses were designed to test the hypotheses that leatherwork and work with solvents are associated with an increased risk of oligozoospermia. The results of the analysis relating to leatherwork will be presented in this section and the result of the analysis for work with solvents will be presented in section 4.7. Whilst the study hypothesis related primarily to oligozoospermia, the effects of leatherwork on motility and morphology were also examined. The results regarding motility and morphology in relation to leatherwork are presented in this section and the corresponding results relating to work with solvents are given in section 4.7.

4.6.1 The relationship between current leatherwork and oligozoospermia

For these analyses the semen analysis results were used to divide the men into 'cases' with oligozoospermia and 'controls' without oligozoospermia. Oligozoospermia was defined as a sperm concentration of 20 million per ml or less [WHO, 1987]. In order to be a case under this definition, oligozoospermia had to be present in all samples tested. Not all of the 1906 men had had a semen analysis carried out. Thus, this analysis is based on the 1580 who had had at least one semen sample tested, had worked at some stage in their life (four excluded) and did not have substantial amounts of missing data for the important variables (two with extensive missing data excluded). The exposure of interest was leatherwork in the current job for those employed or the most recent job for those currently unemployed. There was no difference in the proportion of leatherworkers (15.4%) and the proportion of non-leatherworkers (15.7%) who did not have a semen analysis result available.

In total there were 26 leatherworkers. One worked in a tannery; one worked in coat and jacket fabrication; two worked in handbag manufacture; and the remainder worked in shoe manufacture. This represents a prevalence of 13.6 per 1,000 infertility presenters and 8.72 per 1000 Leicestershire resident infertility presenters. Twenty-two of the 26 were currently employed and four were unemployed at the time of the interview. One of the four had been unemployed for one month, one for four months, one for six and one for 12 months. That is, they all had relatively recent exposure to leatherwork. Of the 26, 16 (61.5%) had primary male infertility compared with 985/1845 (53.4%) of the non-leatherworkers, this difference was not statistically significant (OR 1.38; 95%CI 0.62, 3.06). The mean duration of trying to conceive was similar for the two groups at 34.8 months for the leatherworkers and 33.1 months for the non-leatherworkers. Table 4.6.1 gives the characteristics of the sperm concentration results by leatherworker status. Four of the leatherworkers did not have a semen analysis result available.

Table 4.6.1: Sperm concentration characteristics for leatherworkers and non-leatherworkers (current and most recent job) (n=1580)

Sperm concentration ($\times 10^6$ per ml)	Leatherworkers	Non-leatherworkers
Number of men (n)	22	1558
Mean	62.0	62.7
St Dev	59.7	63.7
Median	50.0	47.5
Range	0 - 239	0 - 565

The results given in table 4.6.1 showed the markedly skewed distribution of sperm concentration in both groups but showed little evidence of a difference in sperm concentration between the groups.

Table 4.6.2 gives the results of the univariate analysis with estimates of the unadjusted risk of oligozoospermia related to exposure to leatherwork (current and most recent job) and a range of other occupational and lifestyle factors of interest.

Table 4.6.2: Unadjusted odds ratios for the risk of oligozoospermia related to leatherwork (current or most recent) and a range of other factors (n=1580)

Exposed to factor Yes:No	Case (Oligospermia) n=367		Control (Not oligospermia) n=1213		Unadjusted odds ratio	95% confidence interval
	n	%*	n	%*		
Leatherwork	5	1.36%	17	1.40%	0.97	0.36, 2.65
Mumps	149	40.6%	510	42.0%	0.94	0.74, 1.19
Illness†	9	2.5%	20	1.7%	1.50	0.68, 3.32
Operations‡	46	12.5%	70	5.8%	2.34	1.58, 3.46
Current medicines ff	9	2.5%	38	3.1%	0.78	0.37,1.62
Past medicines ff	16	4.4%	54	4.5%	0.98	0.55, 1.73
Pelvic/abdominal x-rays	90	24.5%	251	20.7%	1.25	0.95, 1.64
Alcohol consumption:						
Abstainer	49	13.4%	133	11.0%	1.28	0.89, 1.82
>0 - 4.0 units/day	245	66.8%	848	69.9%	1#	
4.01-6.0 units/day	43	11.7%	135	11.1%	1.10	0.76, 1.60
6.01+ units/day	29	7.9%	81	6.7%	1.23	0.79, 1.94
Drinks, vol missing	1	0.3%	16	1.3%	0.22	0.04, 1.32

* Percentage of those exposed to each factor *eg* leatherwork 5/367=1.36%
† Illnesses which may potentially impair fertility (list appendix D)
‡ Operations which may potentially impair fertility (list appendix D)
ff Medicine, current and past, which may potentially impair fertility (list appendix D)
Baseline comparison group

Table 4.6.2 contd: Unadjusted odds ratios for the risk of oligozoospermia related to leatherwork (current or most recent) and a range of other factors (n=1580)

Exposed to factor Yes:No	Case (Oligospermia) n=367		Control (Not oligospermia) n=1213		Unadjusted odds ratio	95% confidence interval
	n	%*	n	%*		
Caffeinated cola/coffee	331	90.2%	1085	89.5%	1.08	0.74, 1.60
Smoking:						
Never	156	42.5%	503	41.5%	1#	
Ex <=2yrs	46	12.5%	166	13.7%	0.89	0.62, 1.30
Ex >2yrs	20	5.5%	63	5.2%	1.02	0.60, 1.75
Current 1-14	66	18.0%	223	18.4%	0.95	0.69, 1.32
Current 15-25	59	16.1%	209	17.2%	0.91	0.65, 1.28
Current 25+	20	5.5%	49	4.0%	1.32	0.76, 2.28
Currently working	336	91.6%	1132	93.3%	0.78	0.50, 1.19
Leicestershire resident	333	90.7%	1007	83.0%	2.00	1.37, 2.92
Social class:						
I & II	95	25.9%	384	31.7%	1#	
III	205	55.9%	587	48.4%	1.41	1.07, 1.86
IV & V & rest	67	18.3%	242	20.0%	1.12	0.79, 1.59
Age group:						
18 - 29yrs	164	44.7%	505	41.6%	1#	
30 - 39yrs	178	48.5%	614	50.6%	0.89	0.70, 1.14
40 - 49yrs	21	5.7%	87	7.2%	0.74	0.45, 1.23
50+yrs	4	1.1%	7	0.6%	1.76	0.51, 6.08
Not married	59	16.1%	185	15.3%	1.06	0.77, 1.46
Work irregular hours	39	10.6%	175	14.4%	0.71	0.49, 1.02
Work in many places	141	38.4%	429	35.4%	1.14	0.90, 1.45

* Percentage of those exposed to each factor *eg* leatherwork 5/367=1.36%
# Baseline comparison group

Table 4.6.2 contd: Unadjusted odds ratios for the risk of oligozoospermia related to leatherwork (current or most recent) and a range of other factors (n=1580)

Exposed to factor Yes:No	Case (Oligospermia) n=367		Control (Not oligospermia) n=1213		Unadjusted odds ratio	95% confidence interval
	n	%*	n	%*		
Workplace not clean	162	44.4%	496	40.9%	1.14	0.90, 1.45
Solvent use (w)†	115	31.3%	388	32.0%	0.97	0.75, 1.25
Glue use (w)	76	20.7%	278	22.9%	0.88	0.66, 1.17
Cleaning agent use (w)	91	24.8%	298	24.6%	1.01	0.77, 1.32
Paint spraying (w)	26	7.1%	87	7.2%	0.99	0.63, 1.55
Colour mixing solns (w)	9	2.5%	33	2.7%	0.90	0.43, 1.89
Photocopy use (w)	129	35.2%	506	41.7%	0.76	0.59, 0.97
VDU use (w)	95	25.9%	413	35.1%	0.68	0.52, 0.88
Microwave use (w)	27	7.4%	106	8.7%	0.83	0.53, 1.29
Welding (w)	32	8.7%	107	8.8%	0.99	0.65, 1.49
Solvent use (h)‡	30	8.2%	116	9.6%	0.84	0.55, 1.28
Glue use (h)	23	6.3%	98	8.1%	0.76	0.48, 1.22
Cleaning agent use (h)	15	4.1%	52	4.3%	0.95	0.53, 1.71
Paint spraying use (h)	12	3.3%	66	5.4%	0.59	0.32, 1.09
Welding (h)	39	10.6%	94	7.8%	1.42	0.96, 2.10
Microwave use (h)	246	67.0%	801	66.0%	1.05	0.82, 1.34

* Percentage of those exposed to each factor *eg* leatherwork 5/367=1.36%
† Exposed at work (w)
‡ Exposed at home (h)

As can be seen from table 4.6.2 the unadjusted odds ratio for oligozoospermia associated with leatherwork was 0.97 (95%CI 0.36, 2.65) which indicates there was little evidence that exposure to leatherwork seriously increased the risk of oligozoospermia. There were five factors with elevated unadjusted odds ratios. These were having a medical condition which may potentially impair fertility (OR 1.50; 95%CI 0.68, 3.32); ever having had an operation which may potentially impair fertility (OR 2.34; 95%CI 1.58, 3.46); ever having had an x-ray of the pelvis or abdomen (OR 1.25; 95%CI 0.95, 1.64); being a Leicestershire resident (OR 2.0; 95%CI 1.37, 2.92); and carrying out welding outside of work (OR 1.42; 95%CI 0.96, 2.10), although welding at work was not (OR 0.99; 95%CI 0.65, 1.49). There were three factors which were apparently protective against oligozoospermia. These were not working regular days (shift work etc) (OR 0.71; 95%CI 0.49, 1.02); using a photocopier (OR 0.76; 95%CI 0.59, 0.97); and using a computer visual display unit at work (VDU) (OR 0.68; 95%CI 0.52, 0.88).

Adjusted odds ratio were derived from unconditional logistic regression models using the two modelling methods outlined in section 3.9.6. First a parsimonious, statistically rational model was derived using the likelihood ratio test to determine if variables significantly affected the fit of the model. Second, a biologically derived model was fitted. This model included terms that were though *a priori* likely to be related to the risk of oligozoospermia on biological grounds. After testing for interactions the terms remaining in the final two models are given in table 4.6.3.

Table 4.6.3: Adjusted odds ratios from the statistical and biological models of the relationship between the risk of oligozoospermia and leatherwork (current or most recent) (n=1580)

Exposure Yes: No	Adjusted odds ratio	95% confidence interval
Statistically derived model:		
Leatherwork (current or most recent)	1.20	0.43, 3.33
Operations*	2.43	1.64, 3.62
Social class III: Rest	1.35	1.07, 1.71
Leicestershire resident	2.02	1.37, 2.96
Biologically derived model:		
Leatherwork (current or most recent)	1.20	0.43, 3.35
Operations*	2.37	1.58, 3.54
Social class III: Rest	1.33	1.05, 1.69
Leicestershire resident	2.09	1.42, 3.07
Illnesses*	1.45	0.63, 3.34
Pelvic or abdominal x-rays	1.21	0.91, 1.62
Medicines - current*	0.70	0.31, 1.58
Medicines - past*	0.90	0.47, 1.72
Age group:		
18 - 29yrs	1.00#	
29 - 39yrs	0.87	0.68, 1.11
39 - 49 yrs	0.73	0.43, 1.22
50+yrs	1.62	0.46, 5.74

* Operations, illnesses and medicines which may potentially affect fertility (appendix D)
# Baseline comparison group

The results given in table 4.6.3 indicate that having adjusted for the various factors given in each model, leatherworkers were 1.20 times more likely to present with oligozoospermia compared to non-leatherworkers. The 95% confidence interval (0.43, 3.33) was wide and included one which indicate that there is much uncertainty surrounding this estimate. In other words the role of chance cannot be excluded.

Using Burton's method, the probability that the true relative risk of oligozoospermia associated with leatherwork was 2.0 or greater was estimated as 0.17 and the probability that the true odds ratio was 0.5 or less was 0.047 [Burton, 1994]. That is to say, there is only a 17% chance that leatherwork leads to a two fold increase (or greater) in the risk of oligozoospermia and only about a 5% chance that leatherwork leads to a halving or more in risk.

Multilevel modelling of the semen analysis results was carried out as this allowed full use of both semen samples when two were provided. This analysis gave a direct mutually adjusted estimation of the effect of leatherwork and the other factors of interest upon the measure of sperm concentration. As the data were markedly skewed a $\log_e (+1)$ transformation of the data was carried out for this analysis. The regression coefficients were exponentiated to convert the results to the untransformed scale for presentation in table 4.6.4.

Table 4.6.4: Estimates of the mutually adjusted effects of leatherwork and other factors upon the sperm concentration results

Factor present: Yes/No	Estimate	95% confidence interval
Model constant*	47.6	39.9, 56.7
Leatherwork	0.94	0.56, 1.59
Operations†	0.51	0.40, 0.64
Social class III: Rest	0.95	0.86, 1.04
Leicestershire resident	0.73	0.61, 0.87

* This is an estimate of the expected sperm concentration (x 10^6 per ml) in men who were 'no' for all four factors in the model
† Operations which may potentially impair fertility (appendix D)

The results in table 4.6.4 indicate that being a leatherworker resulted in only a 6% reduction (estimate 0.94) in sperm concentration compared to not being a leatherworker and this was not statistically significant as indicated by the 95% confidence interval. Of note, having had an operation which was defined *a priori* as being likely to impair fertility or to have been carried out for a condition which may have been associated with infertility, was associated with about a 50% reduction (estimate 0.51) in sperm concentration and this was statistically significant.

4.6.2 The relationship between current leatherwork and low sperm motility

For these analyses the semen analysis results were used to divide the men into cases with low sperm motility and controls who had normal motility. Low motility was defined as having 50% or less motile sperm [WHO, 1987]. In order to be a case under this definition, low motility had to be present in all samples tested. The analyses presented here, like the ones relating to oligozoospermia, were based on the 1580 men who had a semen analysis performed, had worked at some stage in their life and did not have substantial amounts of missing data.

Table 4.6.5 gives the characteristics of the sperm motility results by leatherworker status (current or most recent job). As can be seen there was little evidence of a difference in the sperm motility between the two groups.

Table 4.6.5: Sperm motility (%) characteristics for leatherworkers and non-leatherworkers (current or most recent job) (n=1580)

Sperm motility (%)	Leatherworkers	Non-leatherworkers
Number of men (n)	22	1558
Mean	51%	48%
St Dev	23.5%	22.2%
Median	56%	40%
Range	0 - 92.5%	0 - 95%

A univariate analysis was carried out to estimate the unadjusted risk of low motility associated with exposure to leatherwork (current or most recent job) and the same range of occupational and lifestyle factors used in the oligozoospermia analysis (see table 4.6.2

for the full list of factors). For the sake of brevity and given that motility was not the primary focus of the analysis an abbreviated version of the results giving only those factors which appeared to have some influence on motility is given in table 4.6.6.

Table 4.6.6: Unadjusted odds ratios for the risk of low motility related to leatherwork (current or most recent job) and a range of other factors (n=1580)

Exposed to factor Yes: No	Case (Low motility) n=704		Control (Not low motility) n=876		Unadjusted odds ratio	95% confidence interval
	n	%*	n	%*		
Leatherwork (current or most recent)	5	0.71%	17	1.94%	0.36	0.14, 0.96
Illnesses†	15	2.1%	14	1.6%	1.34	0.64, 2.79
Operations†	70	9.9%	46	5.3%	1.99	1.35, 2.93
Medicines - current†	25	3.6%	22	2.5%	1.43	0.80, 2.56
X-ray of pelvis or abdomen	170	24.2%	171	19.5%	1.31	1.03, 1.67
Leicestershire resident	634	90.1%	706	80.6%	2.18	1.62, 2.93
Microwave use at work	65	9.2%	68	7.8%	1.21	0.85, 1.72
Microwave use outside work	482	68.5%	565	64.5%	1.20	0.97, 1.48

* Percentage of those exposed to each factor *eg* leatherwork 5/704=0.71%
† Operations, illnesses and medicines which may potentially affect fertility (appendix D)

As can be seen from table 4.6.6 the unadjusted odds ratio for low motility associated with leatherwork was 0.36 (95%CI 0.14, 0.96) indicating that leatherwork was, if anything, a factor protecting against low motility. The other factors were all associated with an apparently elevated risk of low motility.

The results of the statistically and biologically derived modelling are summarised below in table 4.6.7

Table 4.6.7: Adjusted odds ratios from the statistically and biologically derived models of the relationship between the risk of low motility and leatherwork (current or most recent job) (n=1580)

Exposure Yes: No	Adjusted odds ratio	95% confidence interval
Statistically derived model:		
Leatherwork (current or most recent)	0.46	0.17, 1.28
Operations*	2.02	1.37, 2.99
Leicestershire resident	2.15	1.59, 2.91
Biologically derived model:		
Leatherwork (current or most recent)	0.47	0.17, 1.30
Operations*	1.97	1.33, 2.94
Social class III: Rest	1.01	0.82, 1.24
Leicestershire resident	2.18	1.61, 2.97
Illnesses*	1.32	0.60, 2.89
Pelvic or abdominal x-rays	1.28	0.99, 1.65
Medicines - current*	1.42	0.74, 2.72
Medicines - past*	0.64	0.37, 1.12
Age group:		
18 - 29yrs	1.00#	
29 - 39yrs	0.92	0.74, 1.11
39 - 49 yrs	1.36	0.89, 2.06
50+yrs	0.93	0.27, 3.13

* Operations, illnesses and medicines which may potentially affect fertility (appendix D)
# Baseline comparison group

Having adjusted for the effects of the factors listed in the table (4.6.7), the odds ratio associated with exposure to leatherwork (0.47) indicated that leatherwork had if anything an apparently protective effect in relation to low sperm motility. The wide confidence interval indicated a considerable degree of uncertainty and included one, that is, the result was not statistically significant. As with the risk of oligozoospermia, having had an operation which may potentially affect fertility was an independent risk factor for low motility and was associated with about a doubling in the risk.

The probability that the true relative risk of low motility associated with leatherwork was 0.5 or less was estimated as 0.56 (56%) and the probability that it was 2.0 or greater was 0.002 (0.2%).

The results of the multilevel modelling analysis indicated that having adjusted for being a Leicestershire resident, fertility affecting operations and being in social class III, comparing leatherworkers to non-leatherworkers, there was an estimated increase in motility of 0.78% (95%CI -8.3%, +9.9%). Having had an operation which may potentially have affected fertility was associated with a 9.6% reduction in motility (95%CI -7.5%, +11.7%).

4.6.3 The relationship between current leatherwork and high sperm deformity

For these analyses the semen analysis results were used to divide the men into cases with a high percentage of sperm deformity and controls who had normal levels of deformity. A high percentage of deformity was defined as having 70% or greater deformed sperm [WHO, 1987]. In order to be a case under this definition, a high percentage of deformed sperm had to be present in all samples tested. The analyses presented here were based on only 1580 men who had a semen analysis performed in which deformity was estimated, who had worked at some stage in their life and had few missing data.

Table 4.6.8 gives the characteristics of the sperm deformity results by leatherworker (current or most recent job) status. As can be seen there was little evidence of a difference in the proportion with sperm deformity between the two groups.

Table 4.6.8: Sperm deformity (%) characteristics for leatherworkers and non-leatherworkers (current and most recent job) (n=1580)

Sperm deformity (%)	Leatherworkers	Non-leatherworkers
Number of men (n)	20	1560
Mean	35%	39%
St Dev	19.1%	20.6%
Median	37.5%	38%
Range	0 - 78.%	0 - 98%

A univariate analysis was carried out to estimate the unadjusted risk of high deformity associated with exposure to leatherwork and the same range of occupational and lifestyle factors were investigated as for oligozoospermia and low motility (see table 4.6.2 for the

full list of factors). Again for the sake of brevity an abbreviated version of the results giving only those factors which appeared to have some influence on deformity is given in table 4.6.9.

Table 4.6.9: Unadjusted odds ratios for the risk of high deformity in relation to leatherwork (current or most recent job) and a range of other factors (n=1580)

Exposed to factor Yes: No	Case (High deformity) n=108		Control (Not high deformity) n=1472		Unadjusted odds ratio	95% confidence Interval
	n	%*	n	%*		
Leatherwork (current or most recent)	2	1.85%	20	1.36%	1.37	0.32, 5.91
Illnesses†	2	4.6%	24	1.6%	2.93	1.10, 7.83
Operations†	15	13.9%	101	6.9%	2.19	1.22, 3.91
Medicines - past†	8	7.4%	62	4.2%	1.82	0.85, 3.90
X-ray of pelvis or abdomen	33	30.6%	308	20.9%	1.66	1.08, 2.55
Leicestershire resident	93	86.1%	1247	84.7%	1.11	0.64, 1.95
Paint spraying	9	8.3%	104	7.1%	1.20	0.59, 2.42
Use of colour mixing solns‡	5	4.6%	37	2.5%	1.88	0.73, 4.89
Solvent use outside work	12	11.1%	134	9.1%	1.25	0.67, 2.33
Glue use outside work	10	9.3%	111	7.5%	1.25	0.64, 2.46
Welding outside work	11	10.2%	122	8.3%	1.25	0.66, 2.40
Microwave use outside work	76	70.4%	971	66.6%	1.22	0.80, 1.87

* Percentage of those exposed to each factor *eg* leatherwork 1/29=3.5%
† Operations, illnesses and medicines which may potentially affect fertility (appendix D)
‡ Solutions

As can be seen from the table (4.6.9) the unadjusted odds ratio for high deformity associated with leatherwork was 1.37 (95%CI 0.32, 5.91). This indicates that leatherworkers had a 37% increased risk of sperm deformity compared to non-leatherworkers, although, as indicated by the confidence interval, this result was not statistically significant. The confidence intervals in general were very wide, this reflected the fact that the analysis was based on only 108 men in the case group. Illness, operations and x-rays were all associated with a statistically significantly increased odds ratios.

The mutually adjusted results from the unconditional logistic regression analyses are given in table 4.6.10.

Table 4.6.10: Adjusted odds ratios from the statistically and biologically derived models of the relationship between the risk of high deformity and leatherwork (current or most recent job) (n=1580)

Exposure Yes: No	Adjusted odds ratio	95% confidence interval
Statistically derived model:		
Leatherwork (current or most recent)	1.65	0.37, 7.30
Operations*	2.20	1.23, 3.93
Social class III: Rest	0.89	0.60, 1.31
Leicestershire resident	1.13	0.64, 1.99
Biologically derived model:		
Leatherwork (current or most recent)	1.74	0.39, 7.77
Operations*	1.90	1.04, 3.47
Social class III: Rest	0.89	0.60, 1.32
Leicestershire resident	1.14	0.64, 2.03
Illnesses*	2.62	0.95, 7.25
Pelvic or abdominal x-rays	1.50	0.96, 2.35
Medicines - current*	0.54	0.15, 2.01
Medicines - past*	1.62	0.68, 3.86
Age group:		
18 - 29yrs	1.00#	
29 - 39yrs	0.92	0.60, 1.39
39 - 49 yrs	1.10	0.51, 2.38

* Operations, illnesses and medicines which may potentially affect fertility (appendix D)
# Baseline comparison group

Having adjusted for the factors listed in the table (4.6.10) the odds ratio associated with exposure to leatherwork indicated that leatherwork was associated with a 65% to 74% increase in high sperm deformity, although neither of the two results were statistically significant. As with oligozoospermia and low motility having had an operation which may have impaired fertility was an independent risk factor for high deformity associated with a doubling in the risk. Of note also, a history of an illness related to fertility was associated with an odds ratio of 2.62, although this result just failed to reach statistical significance as indicated by the 95% confidence interval.

The chance that the true relative risk of high deformity associated with leatherwork was 2.0 or greater was 43%; that it was 2.5 or greater was 32%; and there was a 23% chance that the true relative risk was 3.0 or greater [Burton, 1994]. There was only a 5% chance that the true relative risk was 0.5 or less.

The results of the multilevel modelling analysis indicated that having adjusted for being a Leicestershire resident, fertility affecting operations and being in social class III, comparing leatherworkers to non-leatherworkers, there was an estimated reduction in deformity of only 0.84% (95%CI -9.4%, +7.7%). Having had an operation which may potentially have affected fertility was associated with a 3.5% increase in deformity (95%CI -0.4%, +13.7%).

4.6.4 The relationship between ever having carried out leatherwork and sperm concentration, motility and morphology

The results of the analyses given in section 4.6 so far were all based on the 26 men who were leatherworkers in their current job if they were currently employed or, in their most recent job if they were currently unemployed. In total 71 men currently worked or had worked at some stage in the past as leatherworkers. There was no *a priori* postulated effect of the duration of exposure or duration since exposure. Thus it seemed reasonable to investigate the effects of ever having worked as a leatherworker either currently or at some stage in the past. The men who currently or at some stage in the past worked as leatherworkers were defined as 'ever leatherworkers'. Table 4.6.11 gives the characteristics of the semen analysis results by ever leatherworker status.

Table 4.6.11: Sperm concentration, motility (%) and deformity (%) characteristics for ever- leatherworkers and never- leatherworkers (n=1580)

Semen parameters	Ever-leatherworkers	Never-leatherworkers
Sperm concentration (x 10^6 per ml)		
Number of men (n)	71	1515
Mean	61.8	62.7
St Dev	54.1	64.1
Median	50.0	47.0
Range	0 - 248	0 - 565
Sperm motility (%)		
Number of men (n)	70	1513
Mean	48.4%	68.5%
St Dev	20.2%	22.2%
Median	55.0%	50.0%
Range	0 - 93%	0 - 95%
Sperm deformity (%)		
Number of men (n)	68	1497
Mean	38.8%	38.7%
St Dev	19.4%	20.7%
Median	39.8%	38.0%
Range	0 - 91%	0 - 98%

As can be seen from the table (4.6.11) the sperm characteristics were similar for both groups for all three semen parameters investigated.

Table 4.6.12 gives the results in relation to the risk of oligozoospermia and ever leatherwork from the univariate analysis and the multiple logistic regression analyses for both the statistically and biologically derived models.

Table 4.6.12: Unadjusted and adjusted odds ratios for the risk oligozoospermia* related to ever- leatherwork

Exposure Yes: No	Adjusted odds ratio	95% confidence interval
Univariate analysis: Ever leatherwork	0.80	0.44, 1.46
Statistically derived model: Ever leatherwork#	0.88	0.48, 1.60
Biologically derived model: Ever leatherwork†	0.88	0.48, 1.60

* Cases=oligozoospermia, n=367; controls=not oligozoospermia, n=1213
# Adjusted for the effects of operations (appendix D), social class group and Leicestershire residence
† Adjusted for the effects of operations (appendix D), social class group, Leicestershire residence, illnesses (appendix D), x-rays, medicines current and past (appendix D) and age group

The results given in table 4.6.12 suggest that, having adjusted for confounders, ever having been a leatherwork is associated with a statistically non-significant 12% reduction in the risk of oligozoospermia. Using Burton's method the chance that ever leatherwork is associated with a true reduction in risk of 50% or more was estimated as 6%. The chance that ever leatherwork is associated with a relative risk of 1.5 or greater was estimated as 2% and there is only a 0.14% chance that ever leatherwork is associated with a true relative risk of 2.0 or greater. Having adjusted for social class, operations and Leicestershire residence, comparing ever leatherworkers to never leatherworkers, there is a 7% increase in sperm concentration (95%CI -21%, +45%).

Table 4.6.13 gives the univariate and multiple logistic regression estimates of the relative risk of low motility and high deformity in relation to ever leatherwork.

Table 4.6.13: Unadjusted and adjusted odds ratios for the risk of low motility and high deformity in relation to ever- leatherwork and the probability of the true relative risk being 0.5 or less or 2.0 or greater

Exposure Yes: No	Adjusted odds ratio	95% confidence interval	Prob true RR 0.5 or less	Prob true RR 2.0+
Low motility[1]				
Univariate analysis: Ever leatherwork	0.85	0.53, 1.38		
Statistically derived model: Ever leatherwork*	1.00	0.61, 1.64		
Biologically derived model: Ever leatherwork†	1.00	0.61, 1.65	0.3%	0.3%
High deformity[2]				
Univariate analysis: Ever leatherwork	0.83	0.30, 2.29		
Statistically derived model: Ever leatherwork*	0.88	0.32, 2.45		
Biologically derived model: Ever leatherwork†	0.94	0.33, 2.66	18%	7%

1. Cases = low motility, n=704; controls=not low motility, n=876
2. Cases=high deformity, n=108; controls=not high deformity, n=1472
* Adjusted for operations (appendix D), social class group and Leicestershire residence
† Adjusted for operations (appendix D), social class group, Leicestershire residence, illnesses (appendix D), x-rays, current and past medicines (appendix D) and age group

As can be seen from the table (4.6.13) the results relating to the risk of low motility and high deformity in relation to ever leatherwork were similar to those for oligozoospermia.

There was little evidence from these results that ever leatherworkers were at an increased risk of low motility or high deformity.

The probability values indicated that there was only a 3% chance that the true relative risk for low motility associated with ever leatherwork was 0.5 or less or 2.0 or greater. The values associated with deformity indicated that there was an 18% chance that the true relative risk was 0.5 or less and only a 7% chance that it was 2.0 or greater.

The results of the multilevel modelling analysis indicated that having adjusted for being a Leicestershire resident, fertility affecting operations and being in social class III, comparing leatherworkers to non-leatherworkers there was an estimated reduction in motility of 1.3% (95%CI -6.6%, +3.9%) and an estimated increase in deformity of 2.2% (95%CI -2.7%, +7.0%).

4.7 WITHIN INFERTILITY PRESENTERS ANALYSIS AND DEFINITION OF SET II OF THE CASES AND CONTROLS: SOLVENT WORKERS

Solvent workers were defined *a priori* using a list of occupations associated with solvents. This list was derived from a search of the literature (appendix C). In total 153 men with semen analysis results had current or most recent occupations which fell into this category.

4.7.1 The relationship between work with solvents and sperm concentration, motility and morphology

As with the analyses relating to leatherwork (section 4.6) these analyses were based on the 1,580 men who had at least one semen sample available, had worked at some stage in their life and had few missing data. Cases and controls were defined, as before, on the basis of the results of the semen analysis. Table 4.7.1 gives the characteristics of the semen analysis results by solvent worker (current or most recent job) status.

Table 4.7.1: Sperm concentration, motility (%) and deformity (%) characteristics for solvent workers and those who were not solvent workers (current or most recent job) (n=1580)

Semen parameters	Solvent workers	Not solvent workers
Sperm concentration (x 10^6 per ml)		
Number of men (n)	153	1427
Mean	60.1	63.0
St Dev	64.5	63.6
Median	36.5	48.0
Range	0 - 351	0 - 565
Sperm motility (%)		
Number of men (n)	155	1299
Mean	47.8%	48.6%
St Dev	22.8%	22.1%
Median	50.0%	50.0%
Range	0 - 93%	0 - 95%
Sperm deformity (%)		
Number of men (n)	149	1416
Mean	38.3%	38.7%
St Dev	19.7%	20.7%
Median	39.0%	38.0%
Range	0 - 80%	0 - 98%

As can be seen from the table (4.7.1) the median sperm concentration was lower for solvents workers compared to non-solvent workers. In contrast the motility and deformity results were very similar. Table 4.7.2 gives the results of the unadjusted and adjusted analyses for the risk of oligozoospermia, low motility and high deformity in relation to solvent work (current or most recent job).

Table 4.7.2: Unadjusted and adjusted odds ratios for the risk of oligozoospermia, low motility and high deformity in relation to solvent work and the probability of the true relative risk being 0.5 or less or 2.0 or greater

Exposure Yes: No	Odds ratio	95% confidence interval	Prob true RR 0.5 or less	Prob true RR 2.0+
Oligozoospermia[1]				
Univariate analysis:				
Solvent work	1.28	0.88, 1.87		
Statistically derived model:				
Solvent work*	1.33	0.91, 1.95		
Biologically derived model:				
Solvent work†	1.31	0.90, 1.92	0%	1.5%
Low motility[2]				
Univariate analysis:				
Solvent work	1.08	0.77, 1.51		
Statistically derived model:				
Solvent work*	1.14	0.81,1.61		
Biologically derived model:				
Solvent work†	1.15	0.82, 1.62	0%	0.1%
High deformity[3]				
Univariate analysis:				
Solvent work	1.09	0.57, 2.07		
Statistically derived model:				
Solvent work*	1.14	0.60,2.17		
Biologically derived model:				
Solvent work†	1.13	0.59, 2.18	0.8%	5.1%

1. Cases=oligozoospermia, n=367; controls=not oligozoospermia, n=1213
2. Cases=low motility, n=704; controls=not low motility, n=872
3. Cases=high deformity, n=108; controls=not high deformity, n=1451

* Adjusted for operations (appendix D), social class group and Leicestershire residence

† Adjusted for operations (appendix D), social class group, Leicestershire residence, illnesses (appendix D), x-rays, current and past medicines (appendix D) and age group

As can be seen from the table (4.7.2), compared with non-solvent work, solvent work was associated with about a 30% increased risk of oligozoospermia. This result was not statistically significant. There was a 1.5% chance that the true relative risk was 2.0 or greater and it was highly improbable that it was 0.5 or less. The odds ratios associated with low motility and high deformity were 1.15 and 1.13 respectively. It was highly improbable that the true relative risks for either of these outcomes was 0.5 or less or 2.0 or greater.

By definition the solvent worker group included leatherworkers (appendix C). However, excluding the leatherworkers from the solvent worker group had little impact on the estimates. For example the odd ratio for oligozoospermia changed from 1.33 to 1.31 when the leatherworkers were removed.

The results of the multilevel modelling analysis indicated that having adjusted for being a Leicestershire resident, having had an operation which may potentially affect fertility and being social class III, compared to non-solvent workers, solvent workers experienced an 8.0% reduction in sperm concentration (95%CI -25%,+15%); a 1.4% reduction in motility (95%CI -5.0%, +2.3%); and a 0.4% increase in deformity (95%CI -3.1%, +3.8%).

4.7.2 The relationship between ever working with solvents and sperm concentration, motility and morphology

In total 285 men had at some stage, either currently or at some point in the past, worked in an occupation which fell into the solvent exposed group (appendix C). These men were defined as 'ever solvent' workers. Table 4.7.3 summarises the results of the semen analyses by ever solvent worker status. As can be seen, there was little difference

between the two groups in terms of these results.

Table 4.7.3: Sperm concentration, motility (%) and deformity (%) characteristics for ever solvent workers and never solvent workers (n=1580)

Semen parameters	Ever solvent workers	Never solvent workers
Sperm concentration (x 10^6 per ml)		
Number of men (n)	285	1295
Mean	60.6	63.1
St Dev	61.0	64.2
Median	44.5	48.0
Range	0 - 351	0 - 565
Sperm motility (%)		
Number of men (n)	284	1295
Mean	47.7%	48.7%
St Dev	21.4%	22.4%
Median	50.0%	50.0%
Range	0 - 95%	0 - 95%
Sperm deformity (%)		
Number of men (n)	280	1285
Mean	39.5%	38.6%
St Dev	20.0%	20.7%
Median	39.3%	37.5%
Range	0 - 98%	0 - 98%

Table 4.7.4 gives the results of the unadjusted and adjusted logistic regression analyses in relation to ever solvent work.

Table 4.7.4: Unadjusted and adjusted odds ratios for the risk of oligozoospermia, low motility and high deformity in relation to ever solvent work and the probability of the true relative risk being 0.5 or less or 2.0 or greater

Exposure Yes: No	Odds ratio	95% confidence interval	Prob true RR 0.5 or less	Prob true RR 2.0+
Oligozoospermia[1]				
Univariate analysis:				
Ever solvent work	1.18	0.88, 1.59		
Statistically derived model:				
Ever solvent work*	1.20	0.91, 1.78		
Biologically derived model:				
Ever solvent work†	1.18	0.88, 1.60	0%	0.03%
Low motility[2]				
Univariate analysis:				
Ever solvent work	1.16	0.90, 1.50		
Statistically derived model:				
Ever solvent work*	1.21	0.94,1.58		
Biologically derived model:				
Ever solvent work†	1.21	0.93, 1.58	0%	0%
High deformity[3]				
Univariate analysis:				
Ever solvent work	1.12	0.68, 1.82		
Statistically derived model:				
Ever solvent work*	1.17	0.71, 1.92		
Biologically derived model:				
Ever solvent work†	1.20	0.73, 1.99	0.03%	2.3%

1. Cases=oligozoospermia, n=367; controls=not oligozoospermia, n=1213
2. Cases=low motility, n=704; controls=not low motility, n=872;
3. Cases=high deformity, n=108; controls=not high deformity, n=1451

* Adjusted for operations (appendix D), social class group and Leicestershire residence

† Adjusted for operations (appendix D), social class group, Leicestershire residence, illnesses (appendix D), x-rays, current and past medicines (appendix D) and age group

As can be seen (table 4.7.4), compared with never solvent work, ever solvent work was associated with about a 20% increase in risk of oligozoospermia, low motility and high deformity. However, as demonstrated by the 95% confidence intervals, for none of these results could the role of chance be excluded. Removing the ever leatherworkers from the ever solvent worker group changed the relative risk estimate from 1.20 to about 1.25 for each of the three binary outcomes of interest. However, these results not statistically significant.

The results of the Bayesian analysis indicated that it was highly improbable that the true relative risk was 0.5 or less or 2.0 or greater for oligozoospermia and low motility. There was only a 0.03% chance that the true relative risk associated with high deformity was 0.5 or less and there was only a 2.3% chance that it was 2.0 or greater.

The results from the multilevel modelling analysis indicated that having adjusted for operations, social class and being a Leicestershire resident, compared to never solvent workers, ever solvent workers experienced an estimated 1.0% reduction in sperm concentration (95%CI -16%, +17%); a 1.6% reduction in sperm motility (95%CI -4.5%, +1.3%); and a 1.2% increase in deformity (95%CI -1.5%, +3.9%).

4.8 EXPOSURE TO WORK AS A WELDER

The secondary aim of the work presented in this thesis was to produce an occupation and infertility data set which could be used to test other independent hypotheses. This section of the results will present the findings relating to a test of the independent hypothesis that welding is a risk factor for male infertility [Mortensen, 1988; Bonde, 1993].

Being a welder for the current (most recent) occupation was defined by the single occupational category code 036 [OPCS, 1970]. Being a welder in the current or any past occupation was defined by the category codes 128.00 and 124.06 [OPCS, 1980]. As welding was not of primary concern in the conduct of this study it was not possible to determine, from the occupational details collected, the types of materials welded. There were some men who carried out welding as a peripheral part of their occupation but were not actual welders. There was no material change in any of the results when they were included as welders in the analyses presented below.

4.8.1 Comparison with the perinatal mortality survey controls

The first set of comparisons was with the perinatal mortality control population and was designed to test the hypothesis that welders were at an increased risk of presenting for the investigation of infertility. The cases were defined as all 1606 Leicestershire residents in the infertility study population. The controls were the 1013 perinatal mortality survey (PNMS) control fathers who did not have a history of infertility and whose baby was born in 1985 to 1992 inclusive. Table 4.8.1 gives the case control comparison between the infertility presenters and the perinatal survey controls.

Table 4.8.1: Case control comparison for exposure to work as a welder, comparing infertility presenters as the cases (n=1606) to PNMS controls (n=1013). Leicestershire residents only.

	Welder (current or most recent job)		
	Yes	No	Total
Cases = infertility presenters	13	1593	1606
Controls = PNMS controls	4	1009	1013
Total	17	2602	2619

Odds ratio = 2.06; 95%CI 0.67, 6.34

The odds ratio indicates that infertility presenters were just over twice as likely to be welders (current or most recent job) compared to the controls. However, this result was not statistically significant.

4.8.2 Within infertility presenter comparison: Welders

As with the leatherworkers and solvent workers these analyses were based upon the 1580 men who had at least one semen sample result available, had worked at some stage in their life and had few missing data. Cases and controls were defined by the results of the semen analysis. There was a total of ten men who were currently employed as welders or if currently unemployed their most recent occupation had been as a welder.

Table 4.8.2 gives the results of the semen analysis by welder status (current or most recent job). As can be seen, the median sperm concentration for the welders was just over half that of the non-welders (25 versus 47 $x10^6$ per ml respectively). The median sperm

deformity was also higher for the welders, as was the median motility.

Table 4.8.2: Sperm concentration, motility (%) and deformity (%) characteristics for welders and non-welders (current or most recent job) (n=1580)

Semen parameters	Welders	Not welders
Sperm concentration (x 10^6 per ml)		
Number of men (n)	10	1570
Mean	37.8	62.8
St Dev	27.9	63.7
Median	25.0	47.0
Range	0 - 75	0 - 565
Sperm motility (%)		
Number of men (n)	9	1445
Mean	58.9%	48.5%
St Dev	13.6%	22.5%
Median	60.0%	49.0%
Range	35 -95%	0 - 95%
Sperm deformity (%)		
Number of men (n)	9	1556
Mean	41.2%	38.6%
St Dev	14.3%	20.7%
Median	45.0%	38.0%
Range	20 -60%	0 - 98%

Table 4.8.3 gives the odds ratios from the unadjusted and adjusted analyses for the risk of oligozoospermia, low motility and high deformity in relation to being a welder (current or most recent job).

Table 4.8.3: Unadjusted and adjusted odds ratios for the risk of oligozoospermia, low motility and high deformity in relation to being a welder and the probability of the true relative risk being 0.5 or less or 2.0 or greater

Exposure Yes: No	Odds ratio	95% confidence interval	Prob true RR 0.5 or less	Prob true RR 2.0+
Oligozoospermia[1]				
Univariate analysis:				
Welder	0.82	0.17, 3.88		
Statistically derived model:				
Welder*	0.70	0.15, 3.33		
Biologically derived model:				
Welder†	0.72	0.15, 3.40	32%	9%
Low motility[2]				
Univariate analysis:				
Welder	1.61	0.15, 2.45		
Statistically derived model:				
Welder*	0.58	0.14,2.32		
Biologically derived model:				
Welder†	0.62	0.15, 2.51	38%	5%
High deformity[3]				
Univariate analysis:				
Welder	0	0, 4.86		
Statistically derived model:				
Welder*	#			
Biologically derived model:				
Welder†	#		#	#

1. cases=oligozoospermia, n=367; controls=not oligozoospermia, n=1213
2. cases=low motility, n=704; controls=not low motility, n=872
3. cases=high deformity, n=108; controls=not high deformity, n=1451

* Adjusted for operations (appendix D), social class group and Leicestershire residence

† Adjusted for operations(appendix D), social class group, Leicestershire residence, illnesses (appendix D), x-rays, current and past medicines (appendix D) and age group

\# Not estimated

As can be seen from the table (4.8.3) compared to not being a welder, being a welder was associated with a statistically non-significant 18% to 20% reduction in the relative risk of oligozoospermia and a statistically non-significant 38% to 42% reduction in the relative risk of low motility. There were no welders who were in the high deformity category therefore the estimated odds ratio was zero. The upper limit of the 95% confidence interval for this estimate was 4.86. The chance that the true relative risk of oligozoospermia associated with welding was 2.0 or greater was only 9%, whereas there was a 32% chance that the true relative risk was 0.5 or less. For low motility the corresponding results were 5% and 38%.

The results from the multilevel modelling indicated that having adjusted for operations, social class and being a Leicestershire resident, compared to non-welders, welders experienced a 28% reduction in sperm concentration (95%CI -68%, +61%); a 10% increase in motility (95%CI -4.9%, 25.2%); and a 1.4% increase in deformity (95%CI -13%, +16%).

4.8.3 Within infertility presenter comparison: Ever welders

In total 22 men were either currently employed as welders or had been at some stage in the past. These men were defined as 'ever welders'. Table 4.8.4 gives the results of the semen analysis by ever welder status. As can be seen all three parameters were very similar for both groups.

Table 4.8.4: Sperm concentration, motility (%) and deformity (%) characteristics for ever welders and never welders (n=1580)

Semen parameters	Welders	Not welders
Sperm concentration (x 10^6 per ml)		
Number of men (n)	22	1558
Mean	46.8	63.0
St Dev	46.7	63.8
Median	42.0	47.0
Range	0 - 222	0 - 565
Sperm motility (%)		
Number of men (n)	21	1433
Mean	51.7%	48.5%
St Dev	24.3%	22.5%
Median	57.0%	49.0%
Range	0 - 80%	0 - 95%
Sperm deformity (%)		
Number of men (n)	21	1544
Mean	38.3%	38.6%
St Dev	23.4%	20.6%
Median	39.0%	38.0%
Range	0 - 90%	0 - 98%

Table 4.8.5 gives the odds ratios from the unadjusted and adjusted analyses for the risk of oligozoospermia, low motility and high deformity in relation to ever being a welder.

Table 4.8.5: Unadjusted and adjusted odds ratios for the risk of oligozoospermia, low motility and high deformity in relation to ever being a welder and the probability of the true relative risk being 0.5 or less or 2.0 or greater

Exposure Yes: No	Odds ratio	95% confidence interval	Prob true RR 0.5 or less	Prob true RR 2.0+
Oligozoospermia[1]				
Univariate analysis:				
Ever welder	1.26	0.56, 2.88		
Statistically derived model:				
Ever welder*	1.17	0.51, 2.69		
Biologically derived model:				
Ever welder†	1.17	0.51, 2.70	2.2%	10.4%
Low motility[2]				
Univariate analysis:				
Ever welder	0.68	0.31, 1.48		
Statistically derived model:				
Ever welder*	0.68	0.30, 1.48		
Biologically derived model:				
Ever welder†	0.69	0.31, 1.52	21.5%	0.4%
High deformity[3]				
Univariate analysis:				
Ever welder	1.69	0.50, 5.72		
Statistically derived model:				
Ever welder*	1.70	0.50, 5.78		
Biologically derived model:				
Ever welder†	1.68	0.48, 5.81	2.8%	39%

1. cases=oligozoospermia, n=367; controls=not oligozoospermia, n=1213
2. cases=low motility, n=704; controls=not low motility, n=872
3. cases=high deformity, n=108; controls=not high deformity, n=1451

* Adjusted for operations (appendix D), social class group and Leicestershire residence

† Adjusted for operations (appendix D), social class group, Leicestershire residence, illnesses (appendix D), x-rays, current and past medicines (appendix D) and age group

As can be seen from table 4.8.5 ever being a welder compared to not, was associated with a 17% increase in the risk of oligozoospermia; a statistically non-significant result. Ever being a welder was associated with a 32% reduction in the risk of low motility and there was a 70% increase in the risk for high deformity. None of these results were statistically significant. The chances that the true relative risk of oligozoospermia was 0.5 or less or 2.0 or greater were 2% and 10% respectively. There was a 22% chance that the true relative risk of low motility was 0.5 or less and a 39% chance that the true relative risk associated with high deformity was 2.0 or greater.

Having adjusted for operations, social class and Leicestershire residence, compared to never welders, ever welders experienced a 36% reduction in sperm concentration (95%CI -60%, +2.1%); a 3.1% increase in sperm motility (95%CI -5.2%, +11.4%); and a 0.9% reduction in sperm deformity (95%CI -8.6%, +6.9%).

4.9 HYPOTHESIS GENERATION ANALYSIS

One of the secondary aims of this work was, having created an occupation and infertility data base, to investigate whether other hypotheses could be generated from the data set. This 'fishing expedition' was carried out firstly by describing the frequency of occurrence of each of the 27 occupational groups defined by the OPCS classification of occupations 1970 [OPCS, 1970] in the infertility presenter group compared to the perinatal controls. Secondly, the frequency of occurrence of oligozoospermia, low motility and high deformity for each of the occupational groups [OPCS, 1970], was compared to the frequency of occurrence of oligozoospermia, low motility and high deformity overall. Statistical significance testing was carried out using the standard Chi-squared test of association and Fisher's Exact test where appropriate. Given this was intended to be a hypothesis generation process and therefore was intended to be an inclusive rather exclusive process, the formal level of statistical significance was set at $P<0.10$.

4.9.1 Comparison with the perinatal controls

Five occupational categories occurred with greater frequency ($P<0.10$) in the infertility presenter group than the perinatal controls. The details of the occupations within each category were examined further and only those categories which were represented in excess in the infertility group are presented below.

XII Paper and printing workers (083 - 088):
- 086 Printing press operators
- 087 Printers (so described)
- 088 Printing workers not elsewhere classified

XIV Makers of other products (089 - 092):
- 090 Workers in plastics
- 092 Other production process workers

XX Warehousemen, storekeepers, packers, bottlers (136 -137):
- 136 Warehousemen, storekeepers and assistants

XXI Clerical workers (138 - 142):
- 138 Office managers not elsewhere classified
- 139 Clerks, cashiers, receptionists
- 140 Office machine operators including use of VDUs

XXII Sales workers (143 - 150):
- 143 Proprietors and managers for sales
- 144 Shop salesmen and assistants
- 147 Garage proprietors
- 148 Commercial travellers, financial agents

Group XX (warehousemen and storekeepers) was examined in further detail. However, no particular pattern of industrial employment emerged.

4.9.2 Within infertility presenter comparisons: Oligozoospermia

Two occupational groups were identified as being associated with an excess frequency of occurrence of oligozoospermia. These were:

VII Engineers and allied trade workers (031 - 054):
- 034 Steel erectors, riggers
- 040 Tool makers, tool room fitters
- 045 Plumbers, gas fitters, lead burners
- 046 Pipe fitters, heating engineers
- 048 Metal workers not elsewhere classified
- 051 Goldsmiths, silversmiths, jewellery makers

XI Construction workers (093 - 098)
- 094 Plasterers, cement finishers, terrazzo workers
- 095 Builders (so described), clerks of work

Of note, of the 36 men in the engineers and allied trade workers group, 11 said they undertook welding as part of their work.

4.9.3 Within infertility presenter comparisons: Low motility and high deformity

There were no categories of occupation associated with an excess occurrence of high deformity. One group had an excess occurrence of low motility:

XIV Makers of other products (089 - 092)
- 089 Workers in rubber
- 091 Craftsmen not elsewhere classified

4.10 THE NON-RESPONDERS

In total 55 couples refused to be interviewed in the study, that is both partners declined to participate. A further 224 men refused to be involved although their wives had participated. Overall 9.6% of the eligible men approached at the Leicester Royal Infirmary refused to participate. The percentages were 19.2% for the Leicester General Hospital and 19.8% for Kettering District General Hospital. The figure for Kettering also included the Woodland private patients.

4.10.1 Couple refusers

Apart from the age of the female partner the only other information available about the couple refusers came from the results of the semen analysis. It can be seen from the results summarised in table 4.10.1 that the mean age of the women in the couple refuser group was similar to the mean age of the women who participated and compared to the respondents a similar proportion of couple refusers (85%) had a semen analysis result available. When the results of the semen analyses were compared a similar proportion of the couple refusers fell into the oligozoospermic category, although the median sperm concentration for this group was higher than that of the responder group. A slightly higher proportion of couple refusers had low motility, although this difference was not statistically significant (P=0.069). The medians for the motility percentage were similar for both groups. The deformity results were also similar for both groups.

Table 4.10.1: Characteristics of the couple refusers and the male refusers compared to the respondents

Characteristics	Couple refusers (n=55*/47#) n	%	Male refusers (n=224*/131#) n	%	Respondents (n=1906*/1586#) n	%
Female partners age (yrs):						
Mean	29.05		29.01		28.66	
St Dev	4.97		5.31		4.79	
Range	21 - 45		19 - 45		17 - 46	
Semen analysis result*:						
Yes	47	85.5%	131	58.5%	1611	84.5%
No	8	14.5%	93	41.5%	295	15.5%
Oligozoospermia#:						
Yes	11	23.4%	36	27.5%	369	23.3%
No	36	76.6%	95	72.5%	1217	76.7%
Sperm concentration ($x10^6$ per ml):						
Mean	82.8		54.7		62.7	
Median	61.5		42.0		47.5	
Low motility#:						
Yes	27	57.4%	58	44.3%	710	44.9%
No	20	42.6%	73	55.7%	873	55.1%
Motility (%):						
Mean	44.6%		47.4%		48.5%	
Median	50.0%		52.0%		47.0%	
High deformity#:						
Yes	3	6.4%	10	7.6%	109	6.9%
No	44	93.6%	121	92.4%	1474	93.1%
Deformity (%):						
Mean	39.4%		34.8%		38.7%	
Median	38.0%		30.0%		38.0%	

* Total number of men

This denominator is all those men who had a semen analysis performed. The denominator changed for the motility and morphology parameters for the respondents as these parameters were not estimated in all samples

4.10.2 Male refusers

More information was available for the male-only refusers by virtue of the fact that their female partners had been interviewed. The female partner data for the male non-responders were compared to the female partner data for the male responders. These data are given in table 4.10.2

Table 4.10.2: Information from the female partners for the male non-responders(n=224) compared to the male responders (n=1877)

Characteristics reported by the female partner	Male refusers (n = 224) n	%	Responders (n = 1877) n	%
Marital status:				
Married	146	65.0%	1573	83.8%
Living together	61	27.3%	283	15.1%
Not living together	17	7.8%	21	1.1%
Duration of time together:				
Less than 12 months	5	2.2%	28	1.5%
12 - 23 months	21	9.4%	111	5.9%
24 - 35 months	32	14.3%	231	12.3%
36+ months	166	74.1%	1507	80.3%
Social class*:				
I & II	52	23.2%	405	21.6%
III	107	47.7%	908	48.4%
IV & V	61	27.3%	512	27.3%
Other	4	1.9%	52	2.8%
Type of female infertility:				
Primary	93	41.4%	1036	55.2%
Secondary	131	58.6%	841	44.8%
Duration of trying to conceive:				
Less than 12 months	26	11.4%	120	6.4%
12 - 23 months	57	25.5%	527	28.1%
24 - 35 months	63	28.2%	494	26.3%
36 + months	76	34.1%	730	38.9%
Missing	2	0.9%	6	0.3%

* Social class based on the female partners' occupation

As can be seen from table 4.10.2, the non-responders were less likely to be married than were the responders (OR 0.36; 95%CI 0.03, 0.47) and this difference was statistically significant. The non-responders were 1.64 times (95%CI 1.05, 2.56) more likely to have been together for less than 2 years compared to the responders and this difference was statistically significant. The pattern of female infertility was also statistically significantly different between the two groups with a greater proportion of secondary infertility in the non-responders compared to the responders (OR 1.74; 95%CI 1.33, 2.33). In contrast the duration of trying to conceive was very similar for both groups as was the social class distribution based on the female partners' occupation.

The characteristics of the semen analyses were also compared. These were summarised in table 4.10.1. Compared to the responders statistically significantly fewer of the male non-responders had a semen analysis result available than the responders (58.5% versus 84.5% respectively) (OR 0.26; 95%CI 0.19, 0.35). However, when the characteristics of the results of the semen analysis were compared there were no substantial differences between the male non-responders and the responders.

4.11 SUMMARY OF THE MAIN RESULTS

The main results comparing the infertility presenter group to the perinatal control population are summarised below in table 4.11.1. The main results from the internal comparison for the infertility group relating to the exposure to leatherwork (current and ever), solvent work (current and ever) and welding (current and ever) are summarised overleaf in table 4.11.2.

Table 4.11.1: Main results from the comparison of the Leicestershire infertility presenters with the Leicestershire perinatal controls

Exposure	Unadjusted odds ratio	95% confidence interval
Leatherwork (current or most recent)	1.10	0.46, 2.63
Solvent work (current or most recent)	1.73	1.26, 2.38
Welding (current or most recent)	2.06	0.67, 6.34

Table 4.11.2: Summary of the main findings for leatherwork, solvent work & welding for current (or most recent) and ever exposure

Exposure	Adjusted odds ratio*	95% confidence interval	Prob true OR 0.5 or less	Prob true OR 2.0 or greater	Effect on semen parameter	95%CI
Leatherwork:						
Oligozoospermia / Sperm conc	1.20	0.43, 3.33	4.7%	17%	- 6.0%	-44%, +59%
Low motility / Motility (%)	0.46	0.17, 1.28	56%	0.2%	+0.8%	-8.3%, +9.9%
High deformity / Deformity (%)	1.74	0.39, 7.77	5.1%	43%	-0.84%	-9.4%, +7.7%
Ever leatherwork:						
Oligozoospermia / Sperm conc	0.88	0.48, 1.60	6%	0.01%	+7.0%	-21%, +45%
Low motility / Motility (%)	1.00	0.61, 1.65	0.3%	0.3%	-1.3%	-6.6%, +3.9%
High deformity / Deformity (%)	0.94	0.33, 2.66	18%	7%	+2.2%	-2.7%, +7.0%
Solvent work:						
Oligozoospermia / Sperm conc	1.31	0.90, 1.92	0%	1.5%	-8.0%	-25%, +15%
Low motility / Motility (%)	1.15	0.82, 1.62	0%	0.07%	-1.4%	-5.0%, +2.3%
High deformity / Deformity (%)	1.13	0.59, 2.18	0.8%	5.1%	+0.4%	-3.1% +3.8%
Ever solvent work:						
Oligozoospermia / Sperm conc	1.18	0.88, 1.60	0%	0.03%	-1.0%	-16.0%, 17%
Low motility / Motility (%)	1.21	0.93, 1.58	0%	0%	-1.6%	-4.5%, 1.3%
High deformity / Deformity (%)	1.20	0.73, 1.99	0.3%	2.3%	+1.2%	-1.5%, +3.9%

Table 4.11.2 contd: Summary of the main findings for leatherwork, solvent work & welding for current (or most recent) and ever exposure

Exposure	Adjusted odds ratio*	95% confidence interval	Prob true OR 0.5 or less	Prob true OR 2.0 or greater	Effect on semen parameter	95%CI
Welders:						
Oligozoospermia / Sperm conc	0.72	0.15, 3.40	32%	9%	-28%	-68%, +61%
Low motility / Motility (%)	0.62	0.15, 2.51	38%	5%	+10%	+4.9%,+25%
High deformity / Deformity (%)	0†	0, 4.86	#	#	+1.4%	-13%, +16%
Ever welders:						
Oligozoospermia / Sperm conc	1.17	0.51, 2.70	2.2%	10.4%	-36%	-60%, +2.1%
Low motility / Motility (%)	0.69	0.31, 1.52	21.5%	0.4%	+3.1%	-5.2%, +11%
High deformity / Deformity (%)	1.68	0.48, 5.81	2.8%	39%	-0.9%	-8.6%, +6.9%

* Adjusted for operations (appendix D), social class group III: rest and Leicestershire residence
† Unadjusted estimate
# Not estimated

DISCUSSION

5.1 INTRODUCTION

Before the results from this study are discussed the study design and its implications for the findings will be considered.

5.2 THE STUDY DESIGN

5.2.1 The choice of study design

This study was designed to investigate the relationship between occupational exposure to leatherwork and the risk of presenting with oligozoospermia. The investigation was carried out as a case control study. The use of this design requires discussion.

Generally, in case control studies information about exposures is collected when the outcome is known and thus tends to be subject to bias. Partly as a result of this problem case control studies are often regarded as providing less 'credible' evidence of causality than are cohort studies or randomised controlled trials [Hennekens & Buring, 1987]. However, it would clearly have been inappropriate to contemplate a randomised controlled trial in this setting given that the primary exposure of interest was thought to be potentially deleterious. Nevertheless, a retrospective (historical) cohort study might have been feasible. The reasons why this type of study was not performed merit explanation.

A retrospective cohort study would have involved the identification of a group of leatherworkers as the exposed cohort and a suitable cohort of workers not involved in leatherwork as the unexposed comparison group. The level of exposure could have been quantified for individuals on the basis of details of the nature of the actual work performed;

details of specific substances used, together with the duration of employment [Checkoway *et al*, 1989]. Outcome could have been defined on the basis of the results of semen analysis. Other measures of outcome such as family size in relation to expectations and time to conception could also have been collected.

This type of cohort design was considered, but was not pursued, for a variety of reasons. Access to the exposed population for this study design would have required the full co-operation of the boot and shoe industry as this is the predominant leatherwork industry in Leicestershire. Several approaches were made to the Industry, unfortunately these were not successful.

However, even if access to the leatherworker population had been gained, the other substantial difficulty anticipated was of obtaining semen samples for analysis. The literature on this issue strongly suggests that obtaining semen for analysis outside the clinical setting is very difficult [Hatch & Marcus, 1991; Lähdetie, 1995; Whorton, 1986]. Indeed, as the results from this study show, even when couples present for the investigation of infertility a substantial proportion of male partners (16%) do not produce a sample for analysis. Even in situations where there is good reason to suspect an adverse effect of occupational exposure many men are not willing to produce a semen sample [Whorton, 1986; Hatch & Marcus, 1991; Bonde *et al*, 1996]. For example, in some of the studies of the effects of 1,2-dibromo-3-choloropropane (DBCP), participation was as low as 44% [Whorton *et al*, 1979; Whorton & Foliart, 1988]. Furthermore, non-participation is generally an even greater problem in the non-exposed group [Whorton, 1986; Hatch & Marcus, 1991; Lähdetie, 1995; Bonde *et al*, 1996]. This is illustrated again by the DBCP work where in one study only 22% of the non-exposed group produced a semen sample

[Whorton & Foliart, 1988]. Such levels of non-participation may lead to substantial selection bias; they would inevitably reduce the power of the study if they were not anticipated in the sample size calculations and they may also impair the generalisability of the results.

Had access to the leatherworker population been available, it might have been possible to limit the investigation to a measure of family size and then dispense with the need to collect data from a non-exposed population by using 'standard' general population birth data to calculate standardised fertility ratios. This would have mimicked an external cohort analysis of mortality data using standardised mortality ratios (SMRs) but would have had similar limitations in being unable to adjust for most confounders. An internal cohort comparison might have been possible if a suitable non-exposed cohort had been available. Control of confounding would then have been possible. However, even if these types of investigation had been possible, they would not have provided a direct test of the primary hypothesis.

Thus, given the difficulties outlined, whilst a case control design might be perceived as a less desirable design, pragmatically it was the best approach possible in the circumstances.

5.2.2 The definition and source of cases and controls

This study was designed as a case control study in which cases and controls were defined in various ways with the primary intention of making two sets of case control comparisons. First, the current occupations of the cases of infertility, that is the male respondents resident in Leicestershire in this study, were compared with the current occupations of the

male partners of the control population ('normally fertile' population) from the Leicestershire perinatal mortality case control study (PNMS). Second, in the within infertility presenter analyses, cases were variously defined as having oligozoospermia, low motility or high deformity. These were defined as binary terms using the WHO criteria for abnormal semen parameters [WHO, 1987]. For each of these three categories, the cases were then compared to the remainder who were defined for that purpose as the controls.

Ideally, it would have been preferable to have a sample of men with proven fertility as the control population with which to compare to all the cases presenting with infertility. This would have enabled the question of whether leatherwork is a risk factor for the presentation with infertility to be investigated and confounder data could have been collected and analysed. However, in order to address the primary hypothesis a group of men with oligozoospermia (cases) would need to have been compared to men without this condition (controls). Obviously this would have required semen samples for analysis which returns one back to the problem of the reluctance of men, particularly controls/non-exposed men, to produce semen samples for research purposes. In view of this, the decision was made to use control information which was already available from the perinatal mortality survey as an indirect test of the primary hypothesis. The limitations of these data were that information about male partners was collected from the female partners, the information was limited to only their current/most recent occupation and potential confounder data were not available. Thus, the effects of confounding cannot be excluded in the interpretation of the results from this part of the analysis.

For the purposes of this study, infertility was defined as presentation at one of the specialist infertility or general gynaecology clinics in Leicestershire or Kettering. Every

effort was made to ensure that the Leicestershire data collection arm of the study was population based by ascertaining infertility patients from all central and peripheral clinics held in Leicestershire and by ascertaining Leicestershire patients who attended clinics in the health districts adjacent to Leicestershire. Assurances were given by clinical staff that all Leicestershire private patients were eventually seen in the NHS clinic for some aspect of their assessment. Obviously, however, the possibility remains that some patients were missed. If any were missed they would be more likely to be private rather than NHS patients and thus were likely to be from the higher social classes. This may have resulted in selection bias. However, given that in all probability only a small number of such patients were involved and that infertility did not appear to be related to social class in this population, their exclusion probably had little impact on the study results.

The definition of infertility which was used in the study excluded couples with infertility who had either not presented for medical attention anywhere or had presented to their General Practitioner and had been successfully treated or their infertility had resolved spontaneously without referral for specialist care. This definition, therefore, has obvious limitations. However, pragmatically, it would not have been possible to identify the types of people described above. Furthermore, had it been possible to identify them, it is unlikely that a high level of participation would have been achieved.

A small proportion of men (7.3%) reported having been trying to conceive for less than 12 months, although taking into account the information reported by the female partners the proportion was only 4.5%. On this basis they would not meet formal clinical definitions of infertility as discussed in section 1.3. However, they were not excluded from the data set for several reasons. First, as illustrated above, there was a question over the actual

duration of trying to conceive. There was only 78% agreement overall between the male and female partners as to the duration of trying. Second, these couples had been referred for specialist investigation of infertility and so had for some reason been clinically deemed to have infertility that required investigation. Third, the information collected from those with secondary infertility did not allow the differentiation between those who had previously had primary or secondary infertility (and could legitimately have been referred earlier with secondary infertility) and those who had not. Fourth, early presentation did not appear to have been influenced by the presence of oligozoospermia. Finally, excluding the small group who had been trying to conceive for less than 12 months made no substantial difference to the estimates of relative risk associated with the main outcomes of interest. Whilst it could be argued that the more conservative approach would have been to exclude these men, this would have meant discarding expensively obtained information and would have reduced the study power. Given the definitional uncertainty the decision was made to retain them in the data set.

Recruitment to the study in Leicestershire proceeded rather more slowly than had been anticipated from the pilot work. No reason for this could be identified. A source of additional patients was thus sought and patients from Kettering, Northamptonshire were included from the middle of the second year of the data collection. Kettering was chosen as an additional source as Northamptonshire also has a large boot and shoe industry. Additional advantages were the close geographical location and the fact that Kettering District General Hospital (DGH) has a single consultant who has an interest in infertility and sees all patients with infertility referred to the hospital. Direct access to his private patients was also readily available. These arrangements made patient identification very easy and it was possible to be quite certain that no patients were missed. One

disadvantage was that the population referral base for Kettering DGH could not be easily defined geographically. However, since Kettering patients were only used for the within infertility presenters analyses and referral to Kettering DGH was unlikely to be systematically biased with respect to exposure or outcome, it seemed unlikely that the absence of a geographically defined population base would have resulted in selection bias. The Kettering source contributed important numbers of respondents to the study and thus made a substantial contribution to the power of the study.

5.2.3 The minimisation of information bias

Case control studies are generally prone to recall and interviewer bias [Hennekens & Buring, 1987]. These types of information bias arise because the disease outcome is generally known at the time information about exposures is collected. Several strategies were used in the design of this study in an attempt to circumvent these potential biases. Only newly presenting couples with infertility were included and they were interviewed using structured questionnaires administered in a standardised fashion prior to the instigation of clinical investigations. Thus, the exposure information was collected before the result of the semen analysis was available and thus before the outcome of interest was determined. If the patient's general practitioner had ordered a semen analysis before referral the result was not known to the study team until after the interview when the semen analysis result was sought from the laboratory. In this situation the patient themselves may have known the result. However, it is unlikely that this knowledge would have influenced their responses since the study participants were only informed in general terms about the nature of the study and the specific occupational exposures and outcome of interest were not mentioned. Thus, whilst the interviewers were not blind to the hypothesis, given the sequence of events it is difficult to see how they could have

influenced the collection of exposure data to produce serious interviewer bias. As regards recall bias, since the whole group interviewed were presenting with infertility their recall is likely to have been equally vigilant. Thus the within infertility presenter analyses are unlikely to have been biased by differential recall.

In contrast, however, the information about the fathers of the control babies in the Leicestershire perinatal mortality study was collected in a different way from the infertility presenter data. The information was reported by the mother and was therefore necessarily limited in detail. Whilst it is likely to be less accurate than information collected directly from the men, it seems unlikely that this would have resulted in serious bias, although non-differential misclassification may have occurred.

In summary therefore, whilst the presence of information bias cannot be categorically excluded, it seems likely that the design of the study led to the minimisation of this type of bias.

5.2.4 The response and the effects of non-response

During the course of the study a total of 1,906 men and 2,123 women were interviewed. These figures represent 88.5% and 97.2% of the eligible population of men and women respectively.

The response by over 97% of the women was excellent. The reasons for the differences in response between the men and women is likely to relate to the differing perceptions that men and women have about infertility and its possible causes together with the psychological impact that this diagnostic label can have. Whilst the primary focus of this

study was male infertility, there is still a perception that infertility is a 'woman's problem' [Jequier, 1993; Cummins & Jequier, 1994]. Couples with infertility are generally referred for a gynaecological opinion. Thus, for the purposes of this study it was necessary to recruit participants through gynaecology clinics.

Women not infrequently attended for the appointment alone and 97% were willing to participate in the study. Approaching their male partner was rather more difficult. If the male partner did not attend for the clinic appointment the approach was necessarily rather less personal and there is little doubt that this had an impact on the response. In addition, those not attending the clinic with their wives/partners were possibly less interested in participating in the study for the same reasons they chose not to accompany their wife/partner to the appointment. Given the nature of the topic and the issues discussed above, 88.5% was a very respectable response. Nevertheless, the possible effects of non-response require exploration.

Male non-responders accounted for 11.5% of the total population of men eligible for inclusion in this study. For just over 20% of the non-responders neither of the partners had been interviewed, that is the female and male partner had both refused to participate. For the remaining 80% the female partner was interviewed but the male partner refused. The characteristics of the non-responders were compared to the responders using very limited information from the medical records. In particular, there was insufficient occupational data available in the medical notes for it to be of any material value.

For the situation where both members of the couple had refused to participate the limited comparison information amounted to the female partner's age and semen analysis results.

On comparing these characteristics the couple refusers were remarkably similar to the responder group. Thus, on the basis of this very limited information it seems unlikely that the self-exclusion of these potential participants would have seriously biased the study results.

In contrast, the men who refused to participate when their partners had agreed to be included were different from the respondents for a number of the characteristics that were available for comparison. The non-responders were over twice as likely to be living with their partner rather than married to them, although, they had on average been together for the same length of time. They were 75% more likely to have female secondary rather than primary infertility. There were no statistically significant differences between the groups in terms of the female partner's age, social class and manual versus non-manual occupation. However, the non-participants were nearly four times more likely to not have a semen analysis result available than the respondents (41% versus 16% respectively). Of those who had a semen analysis result available the non-respondents were slightly more likely to have had oligozoospermia than the respondents (27% versus 23% respectively), but this small difference was not statistically significant. Similarly the median sperm concentration was lower in the non-responder group but again was not statistically significantly so. There were no substantial differences in the sperm motility and deformity results between the two groups.

In summary, on the basis of the limited information available, there appeared to be some differences in the characteristics of the non-participants compared with the participants, although these differences appeared to be confined to those men whose partner had participated. Although there were no data available with which to test the proposition, it

seems intuitively unlikely however, that participation was influenced by occupational exposure. On balance therefore is seems unlikely that non-participation led to substantial selection bias, although because of limited information this cannot be ruled out completely.

5.2.5 The use of semen parameter results to define outcome

As illustrated in the review by Rosenberg *et al* [1987] reproductive outcomes in relation to the occupational exposures of women have been quite extensively studied. This probably reflects both the perceived primary role of women in relation to reproduction and the fact that reproductive end points are more easily defined for women than men [Schrag & Dixon, 1985].

Semen samples are a relatively readily available source of information about testicular function. However, the ability to actually predict reproductive capacity from the results of semen analysis is limited [Schrag & Dixon, 1985; Polansky & Lamb, 1988; Lähdetie, 1995, Bonde *et al*, 1996]. Whilst there is a general relationship between low sperm concentration and quality and decreased fertility, a clear correlation between semen parameters and fertilising capacity has not been consistently described [Lähdetie, 1995; Bonde *et al*, 1996]. Azoospermia is the only unequivocally valid and reliable fertility predictor; when present, it of course predicts sterility. Some authors have found a relationship between sperm concentration, motility and morphology, whilst others have not [Bonde *et al*, 1996]. However, this may be in part explained by the fact that most of the data examined comes from studies in infertility clinics with few data coming from general population studies.

A further problem arises from the fact that individuals demonstrate considerable test to test variability in semen parameters and it is for this reason that clinical assessment of semen

involves two or more independent samples [Tielemans *et al*, 1997]. Added to the underlying biological variability [Schrader *et al*, 1988] is the measurement variability that appears to be inherent to semen analysis [Lähdetie, 1995]. In the process of external quality control in ten laboratories using eight samples, Neuwinger *et al* [1990] found a mean coefficient of variation (CV) for sperm concentration of 38% and the CV values ranged from 23% to 73% for high to low concentration samples. The subjective component of the assessment is even greater for the assessment of morphology and motility as illustrated by the morphology assessment, where the CV values ranged from 25% to 111%. For the motility assessment the CV value (9%) was the lowest for immotile sperm and the mean CV value for motility overall was 21%. Despite the best efforts of the World Health Organisation to produce objective standards, experience shows that all of these problems of analysis can be compounded by the setting in which the analyses are performed and the seniority (or otherwise) of the technician [WHO, 1987; Jequier, 1986].

In a series of mathematical simulations, Tielemans *et al* [1997] have shown that the intra-person variability (both biological and measurement) of semen parameters leads to substantial underestimation of odds ratio estimates when semen parameters are used to classify individuals as either cases or controls, although using two semen samples reduces the extent of the underestimation. Thus, intra-person variability has important implications as it reduces the power of a study to detect an effect if in reality one exists. Tielemans *et al* [1997] also suggest that the problem of intra-person variability might also explain the inconsistency of the results of studies looking at the prognostic value of semen parameters in terms of fertility.

The introduction of computer-assisted semen analysis (CASA) was heralded as the objective solution to the problems associated with manual analysis, particularly for the assessment of sperm movement. However, studies have shown that whilst in some circumstances CASA measurements are more consistent than manual measurements [Holt *et al*, 1994] the consistency depends upon the conditions of operation and sample handling [Holt *et al*, 1994; Johnson *et al*, 1996]. Furthermore, Krause [1995] argues that improved precision and reproducibility does not necessarily increase the predictive value of the semen analysis in terms of fertility prognosis. On the other hand other authors disagree [Irvine *et al*, 1994]. A recent consensus workshop held by the European Society for Human Reproduction and Embryology (ESHRE) concluded that "it was generally accepted that the primary use of CASA instruments in diagnostic andrology should be sperm motility analysis, ... not as automated semen analysers to measure total sperm concentration and percentage motile." [ESHRE, 1996].

Assays of semen quality either by standard microscopic techniques or by using CASA cannot detect certain causes of male infertility. As discussed by Levine *et al* [1980] "If, for example, sperm lack the enzymes needed to penetrate the outer membrane and fuse with an egg, an adequate number of well-formed, normally motile sperm will be incapable of fertilization." The presence of genetic damage to the sperm cells will also not be evident unless the damage is expressed in terms of sperm concentration, motility or morphology [Schrader, 1992]. Levine *et al* [1980] also point out that a semen specimen only gives a cross-sectional view of reproductive function, it gives no information about past reproductive ability and unless it is azoospermic it gives little information about future function.

The semen analysis results used in this study were all derived from standard microscopic assessment. The majority were analysed in the Leicester Royal Infirmary Microbiology Department and the second largest group came from Kettering District General Hospital Pathology Department. A small number of results came from elsewhere. Although each laboratory did not have a single consistent observer the staff followed the written protocol for each laboratory. Outcomes for the study were based on oligozoospermia, low motility and high deformity criteria [WHO, 1987].

The semen analysis results were divided into those relating to Leicestershire residents and those to non-Leicestershire residents. Whilst there would have been some misclassification this division would have broadly divided the samples into those analysed in Leicestershire in the Leicester Royal Infirmary microbiology department and those not analysed there. There were clear differences between the results for the Leicestershire residents compared to the rest. The Leicestershire resident results were consistently poorer for all three parameters and this was reflected in the greater proportion of men assigned to each of the oligozoospermia, low motility and high deformity categories. Given the consistency of the differences between the Leicestershire residents and the non-residents the most likely explanation for the differences was differences in methods and standards used in the two major pathology centres rather than a true underlying biological differences. In order to take this effect into account a binary term defining place of residence (Leicestershire residence: Yes/No) was included in all adjusted analyses.

As discussed above, when the binary terms were used, outcome misclassification would inevitably have occurred. However, it seems inherently unlikely that the misclassification would have been biased with respect to the occupational exposure of interest. Such non-

differential misclassification would therefore have led to attenuation of relative risk estimates towards the null, thus risking a failure to detect differences that in reality exist.

Thus, given all the difficulties discussed so far, the question remains whether oligozoospermia was a suitable measure upon which to base the primary hypothesis in this study. Despite the recent advances in andrology and the enormous research effort to devise tests of male fertility and sperm function, semen analysis remains the single most useful biological measure of testicular function that can be applied on a large scale [Lähdetie, 1995; ESHRE, 1996]. Certainly in terms of epidemiological studies other more invasive investigations such as testicular biopsy are clearly untenable and other advanced tests of sperm function would be impractical in terms of the cost [ESHRE, 1996]. Tielemans *et al* [1997] note that ".... our understanding of biological mechanisms is so limited that there is no clear rationale for the choice of a given parameter. The varied pathways through which semen can be affected makes such choices difficult." Thus, they advise that " .... studies focusing on risk factors for male infertility should include an array of semen parameters." Following the hypothesis of this study the analysis concentrated on oligozoospermia as the outcome of primary interest, however, the other available semen parameter results were also examined.

In the debate about the research value of semen analysis results, the differences between the questions asked by clinicians and the questions asked by epidemiologists must not be forgotten. As Lamb & Bennet [1994] state: "epidemiologists ask a different question [to clinicians] when they use semen analysis to screen for toxicants." A tool which has limited use clinically for the counselling of individuals may well be useful in evaluating effects which are important in population terms. For example, using empirical data which included

both fertile and infertile men, Meistrich & Brown [1983] modelled the risk of infertility predicted by sperm concentration. They found that a 50% reduction in sperm concentration in one of the populations they studied would increase the proportion of male infertility from 15% to 19%. In population terms this would represent a substantial effect.

In the context of epidemiological investigations of male fertility the alternatives to semen analysis include the functional assessments of the comparison of fertility rates and time-to-conception studies. The main advantages of these types of studies over studies involving biological samples is that they are non-invasive and thus often attract a high response [Levine *et al*, 1980; Baird & Wilcox, 1986]. Their role in occupational toxicological surveillance is particularly important [Levine *et al*, 1980; Wong *et al*, 1985; Wyrobek, 1993]. Nevertheless, semen analysis has some advantages over these less invasive approaches. Semen analysis allows the examination of men's fertility independently of that of their partners and the social, cultural and biological factors involved in fertility. It is possible to monitor changes with different levels of exposure for the same person and in some circumstances to detect adverse effects ahead of alterations in fertility [Levine *et al*, 1983; Bonde *et al* 1996]. Furthermore, the reproductive function of men who do not have a partner and men whose wives are beyond the childbearing age cannot be ascertained using fertility rates and time-to-conception studies. In a publication from the United States Environmental Protection Agency, Wyrobek and his colleagues [1983] discussed the advantages of semen analysis over experimental data. They pointed out that sperm tests "measure effects of chemical exposure in vivo. This helps minimise the artifacts (tissue penetration, metabolism, pharmacokinetics and dosage) that may be encountered in nongonadal human cells, in nonhuman whole-animal studies, in cultured mammalian cells or in nonmammalian systems."

Thus, in summary it seems that although semen analysis results have limitations as a research tool they are in fact the only practical tool which is currently available which we can use to investigate the direct impact of exposures on male fertility in the epidemiological context.

5.2.6 Definition of exposure

Job title or industry is commonly used as a proxy for exposure in studies of potential occupational hazards [Hatch & Marcus, 1991]. Sever [1995] raises some concerns about the use of job title to "indicate assumed tasks, which are used as surrogates for exposures to specific agents." As he points out job titles may differ with respect to specific substance exposure in different industries and at different time periods. "The same job title in different locations and at different times may reflect considerable heterogeneity in exposure" [Sever, 1995]. In contrast, Floderus [1996] argues that whilst job titles themselves have no aetiological significance, in some circumstances because of day to day variation in exposure levels, job titles may be better markers of long term exposure than direct work place measurements. Indeed in situations where there is no clear hypothesis about which exposure to investigate, Kennedy [1994] suggests that "It is prudent to prescribe a more generic job classification that encompasses most jobs in which the suspected exposures may occur."

The major problem with proxy measures of occupational exposures is the resultant misclassification which can be substantial. The misclassification is generally non-differential with respect to outcome and therefore tends to lead to the attenuation of the relative risk estimates [Linet *et al*, 1987]. This can result in exposures, which are in reality adverse, not being identified. This effect was illustrated by Holmberg & Hernberg [1979] in

a study of different methodological approaches in the investigation of the relationship between exposure to organic solvents and malformations of the central nervous system (CNS). When direct assessment of exposure to solvents was used, an association with CNS malformations was shown. In contrast, when an industrial classification was used as a proxy for exposure the association disappeared. Given the direct evidence it is likely that there *was* an association which was undetected in the indirect analysis because of the effects of misclassification. However, the researchers made no attempt to identify and examine the risks associated with job titles known to be associated with occupational exposure to solvents.

Proxy exposure measures are also non-specific in the sense that having identified an 'at-risk occupation' the actual source of the risk and thus routes for its removal or amelioration are unlikely to be identified. However, given the effects of possible non-differential misclassification, if particular occupations are identified as being associated with an adverse outcome, in an analysis based on job titles, then those occupations would certainly merit more detailed investigation.

In the present study the hypothesis specifically related to leatherwork and it was postulated *a priori* that any adverse effects of leatherwork would be related to exposure to solvents rather than to leather or leather substitutes themselves. Leatherwork describes a very specific occupational group and it seems unlikely that someone who was a leatherworker would report their occupation in such a way that it would appear to be something other than leatherwork. In other words, false negative misclassification by occupational reporting seems intuitively unlikely. Necessarily, jobs which involve working with leather as a peripheral component and therefore not described as leatherwork, would

not have been included. However, in order for omission of this group to have had an effect on the inferences drawn, these types of jobs would have to have had a strong association with oligozoospermia. This seems very unlikely unless the leather and associated substances in those types of jobs were handled in a different more 'adverse' way. Otherwise it would paradoxically imply that lower levels of exposure have more adverse effects than the more constant exposure associated with work that is actually described as leatherwork.

Reliability is a measure of the consistency of information when it is collected more than once; it is sometimes referred to as repeatability [Abramson, 1990]. The reliability analysis of the coding for leatherwork produced a Kappa statistic of 0.87 indicating good agreement between the two independent coders. Six workers were not coded by the first coder as leatherworkers but were by the second. Review of the details of the occupational histories of each of the six showed that they clearly had hands-on leatherwork exposure during their usual working day even though their job title did not necessarily immediately suggest this to be so, for example, a technical manager in a tannery. Following the review of the occupational histories all six were regarded as leatherworkers. It seems unlikely, therefore, given the extent of occupational details collected and the double coding carried out in this particular study that serious misclassification, is likely to have occurred. Furthermore, if it had occurred, its impact is unlikely to have been substantial.

The reliability of the general data collection procedure was subject to a limited assessment. The results suggested that the data collection method had a high reliability. This does not, however, imply anything about the validity of the information collected. There was no means available by which the validity could have been assessed for the

vast majority of the data items collected and no attempt was made to do so.

A general assessment of the reliability of the coding was carried out by blind double coding of social class, socio-economic group and the general occupational coding of the current (or most recent) occupation. A high level of reliability was demonstrated especially when the 1970 classification of occupation [OPCS, 1970] was used. No systematic differences between coders were observed.

In contrast to the situation for leatherworkers, misclassification is likely to have been a greater problem for the definition of work with solvents and for welders. Compared to leatherwork, work with solvents was a much more difficult group of jobs to define on the basis of job title. The job titles used to define work with solvents were derived from a search of the literature and were then coded using both the 1970 and 1980 classifications of occupation [OPCS 1970, 1980]. The definition and the assignment of codes was carried out prior to data analysis and were therefore not data led. Thus, whilst misclassification is likely to have occurred it is likely to have been non-differential and thus would have resulted in the attenuation of relative risk estimates.

Being a welder is a very specific occupation and it has very specific occupational codes in both the 1970 and 1980 classifications. The reliability of the coding of being a welder was very high. Nevertheless, as with leatherwork, misclassification may very well have arisen from the fact that other occupations may involve carrying out substantial amounts of welding but without the welding being the central task and thus title of the job; for example in car repair. This possible effect was examined to the extent that a specific question about welding was asked. In fact, combining welders with those men who were not welders but

who carried out welding made no material difference to the results.

5.2.7 Data quality

Issues of data quality in relation to the reliability of data collection and coding are discussed above. This study involved the collection and handling of extensive amounts of data. Inevitably data handling errors would have occurred. Attempts were made to minimise this effect by double data coding, although this was not blind, and double data entry which was blind. Direct comparison of the two data files enabled differences to be identified and reconciled by reference to the questionnaires. The data set cleaning continued with the cross tabulation of logically related variables and checking against the questionnaires when inconsistencies were identified. It is likely, however, that even after these processes were complete there were remaining random errors in the data. However, given the efforts to ensure data quality, it is likely that these errors were few in number and they would probably have had a minimal impact on the results of the study.

5.2.8 Data analysis

The test of the primary hypothesis was carried out using the data from the infertility study population alone. This approach is akin in concept, although not analysis, to the use of proportional mortality ratios in the sense that it represents a 'within group analysis' where all the group have pathology. In proportional mortality ratio analyses, the comparison is generally of whether a particular occupational group has experienced an increased mortality proportion from a particular cause compared with all other occupational groups. Similarly the 'within infertility presenter' analyses in this study were of a 'diseased' group (defined as presenting complaining of infertility) in which the risk of occurrence of a particular form of the 'disease', namely oligozoospermia, in a specific exposure

(leatherwork) group was compared to the risk in the rest of the group who were not exposed (non-leatherworks). That is, all the comparisons occurred within the context of disease. This is in contrast to the usual case control situation where controls are a non-diseased population whose exposure experiences are compared to the exposure experiences of the diseased group (cases). This approach whilst not novel [Mortensen, 1988] is not commonly used.

The general analytical approach was based on two strategies. The first used the binary division of the semen analysis parameters (*eg* oligozoospermia) and the second used a direct adjusted estimate of the percentage change in each semen parameter related to the exposure of interest.

The binary division approach was used, primarily, because the primary hypothesis required an estimate of the relative risk of oligozoospermia associated with leatherwork. The power of this analysis would have be relatively high if causal pathways to oligozoospermia are totally separate from causes of other types of infertility. This is because in focusing on the infertile group (*ie* the infertility presenters alone) one reduces the random noise which otherwise differentiates fertile people from infertile people. However, if all types of infertility have similar causes then there will be little power in this type of analysis. The reality of the situation probably lies somewhere between the two extremes.

Two approaches were taken to the modelling used to produce adjusted odds ratio estimates for the binary outcomes. The 'statistical' approach relied primarily on the impact various factors had on the statistical fit of the data during the modelling process. This was

something of a mechanistic process for many of the analyses, although only factors which potentially confounded the disease exposure relationship were included. However, in many situations, these factors were probably not confounding the disease exposure relationship substantially as their inclusion had little impact on the odds ratio estimate. For example, the unadjusted odds ratio for oligozoospermia in relation to ever leatherwork was 0.80. Having adjusted for operations, social class and Leicestershire residence status the odds ratio was 0.88. In itself, however, this issue is of minor importance. In a study of reasonable size it is far more costly to miss out an important confounder that to include an unnecessary term in the regression model.

The second 'biologically' based approach involved the construction of a model including terms which were thought likely to be potential confounders on strong *a priori* clinical or biological grounds because of a known or postulated relationship with the outcomes, oligozoospermia, low motility and high deformity. Interestingly, in most analyses there was remarkably little difference in the odds ratio estimates derived from the two different methods. Although other explanations are possible, this implies that it is likely that there is little confounding associated with the additional terms included in the biologically based model.

Both these analytical approaches involved the use of unconditional multiple logistic regression which is a standard analytical tool for the analysis of unmatched case control studies [Breslow and Day, 1980]. As will be discussed later, the use of the Bayesian method of subjective posterior probability calculation described by Burton [1994] was particularly important in this study as it enabled a more informative interpretation of 'negative' findings.

The second analytical strategy involved the use of multilevel modelling [Goldstein, 1987]. This approach provided an appropriate method of dealing with the fact that some men in the analysis had two semen sample results and some had only one. This approach was valid since it is common clinical practice to request two independent samples prior to clinical review of those results. Thus, the subjects and their doctors would be very unlikely to know the first test result at the point at which the patient produced or failed to produce a second sample. As a consequence, the missing second samples can be viewed as missing at random.

Multilevel modelling dealt with the response data in a continuous rather than binary fashion and as such provided more powerful analyses than those based on the binary divisions of the data. A further advantage of this method of analysing the data was that it allowed for the examination of changes in the semen parameters that may not yet have been translated into an increase in the proportion of men in the 'poor outcome' binary groups *ie* the oligozoospermia, low motility and high deformity groups.

5.3 THE CHARACTERISTICS OF THE STUDY POPULATION

The study population was derived from the population of Leicestershire and the catchment population for infertility referrals to Kettering District General Hospital. There were no major differences in the characteristics of these two populations other than the semen analysis results, the implications of which were discussed in section 5.2.5. Thus, for the 'within infertility' presenter analyses both groups were analysed together. Because the geographical base of the Kettering patients could not be defined it was not possible to make comparisons with census data. It was possible, however, to make such comparisons for the Leicestershire residents.

The age distribution of the Leicestershire residents within the age range 20-44 years was similar to the general population of Leicestershire. In contrast, there were some differences in marital status, place of birth and current employment status when the Leicestershire infertility presenters were compared with the general population. A greater proportion of the Leicestershire infertility presenters were married compared to the general population (84.7% versus 56.7% respectively), a greater proportion were currently working (91.6% versus 85.6% respectively) and there were relatively fewer students (0.7% versus 3.3%). All of these factors probably reflect the fact that the infertility presenters were hoping and planning to have a baby and in all probability had tired to ensure that they were secure both financially and emotionally before embarking upon this course of action. A greater proportion of the infertility presenters were born in the Indian Sub-continent and Africa (the majority of whom would ethnically also have been Indian) compared to the general population (18.8% versus 5.9%). This may reflect a higher cultural importance placed on having a baby. Alternatively it may be a consequence of the younger mean age of the immigrant population. Interestingly, there was little variation between the infertility presenters and the general population in terms of social class and socio-economic group based on occupation. This suggests that infertility is a condition which affects all sections of our society.

5.3.1 Occupational exposures

Looking at all the infertility presenters, the occupational characteristics of those currently working were compared to the characteristics of the last job for those unemployed, retired or students who were not working at the time of the interview but had worked in the past. The most striking difference was that those not working were more likely to have had a 'dirty' manual job.

The other characteristics of primary interest were contact with solvents, glue use and use of paints, both at work and outside work. The types of substances reported and the frequencies of the use which was reported and subsequently coded into binary variable (Use: Yes/No) were very variable. For example they ranged from the use of liquid paper white-out in the office to heavy industrial exposure by painters. Thus, solvent exposure defined from these three variable was not used in the construction of the 'solvent work' variable which formed the basis of the analyses of the effects of solvents.

Similarly, welding reported by nearly 9% of men was not used in the definition of the 'being a welder' variable as it included a range of minimal to quite extensive exposure to welding in the context of jobs where welding was a peripheral component of the job *eg* car repairers. In fact, when welding was included in the analysis with the defined welders variable it made no material difference to the results.

5.3.2 Medical conditions

A wide range of medical conditions and operations were reported. It was decided that the most sensible approach to dealing with such a heterogeneous and long list of conditions was to divide them into conditions which may potentially impair male fertility. This was done by reference to standard texts. Care was taken to ensure that treatments, for example, operations which were likely to be therapeutic in terms of infertility were not included. To have done so would potentially have led to an outcome being treated as an exposure.

5.3.3 Lifestyle factors

Questions about cigarette smoking and alcohol consumption were included. The data were compared to General Household Survey (GHS) data for 1992. The data for cigarette smoking were remarkably similar in the two groups. It is difficult to know how to interpret this, as one might expect that experiencing difficulty conceiving might lead to people quitting smoking as a non-specific health measure and they may even have been advised to do so. If this was the case then a high proportion the infertility presenters may have smoked in the past. Alternatively, infertility may lead to stress and anxiety which may lead to smoking. In contrast, over three times as many infertility presenters (12% versus GHS 4%) reported currently abstaining from alcohol. There were also fewer heavy drinkers (7% versus 12% GHS). Again it is difficult to know how to interpret this.

5.3.4 Prevalence of leather work and oligozoospermia

During the planning phase of the study a review was carried out of semen analysis results processed by the microbiology department over a three month period. From this it was estimated that the ratio of oligozoospermia to normal sperm concentration would be 50:50. A recent re-review of those review data confirmed this findings. It was also estimated from the controls in the Leicestershire perinatal mortality survey that the prevalence of leatherwork in the Leicestershire male population of reproductive age was 13 per 1000. These figures were used in the power calculations for the sample size estimates.

During the course of the study, amongst the 1580 men with semen analysis results available, 367 (23%) were found to have oligozoospermia. This represents a ratio close to 25:75 (oligozoospermia: normal concentration). One possible explanation for the lower prevalence is that the semen analysis results reviewed prior to the study related

predominantly to single results for each individual. In the study when two results were available oligozoospermia had to be present in *both* samples in order to classify an individual as oligozoospermic. Regression to the mean on second sample testing would be anticipated. The possibility that this had happened was tested by recalculating the prevalence of oligozoospermia based on only the first sample result. This changed the ratio to 30:70. Thus, whilst regression to the mean partly explains the difference between the two sets of results, it clearly is not the entire explanation. The remaining difference remains unexplained.

The prevalence of leatherworkers in the Leicestershire resident population was only 8.72 per 1000 which was substantially less than the expected 13 per 1000. The explanation for this was quite simply the decline in the boot and shoe industry during the recession in the late 1980s and early 1990s. This was concurrent with the period of the study. As discussed in the methods (section 3.9.3). This change in occupational distribution also meant that fewer years of the perinatal control data could be used as comparison data. Both these factors had important implications for the study in terms of its power. In fact the study was originally designed with 500 cases and 1500 controls in order to have 90% power to detect at $P<0.05$ a relative risk of 3.0 in the comparison with the perinatal controls. In fact, the comparison was between 1606 cases and 1013 controls and thus would have only had 69% power to detect a relative risk of 3.0 and 80% power to detects a relative risk of 3.5 at $P<0.05$. In the event the estimated relative risks were much smaller that 3.0, and to detect as 'significant' relative risks as small as those observed would have required a huge study.

For the within infertility presenter analysis, the study was designed to have 90% power to detect a relative risk of 3.0 (<0.05) with 1000 cases and 1000 controls. However, the comparison populations comprised 367 cases (with oligozoospermia) and 1213 controls, with a lower than expected prevalence of exposure to leatherwork. Thus, the study only had 57% power to detect a relative risk of 3.0 and 80% power to detect a relative risk of 4.25 at P<0.05. Again, the estimated relative risks were much smaller.

5.4 LEATHERWORK

In this section all the results relating to the investigation of the primary hypothesis of leatherwork as a risk factor for oligozoospermia and presentation with infertility will be discussed.

5.4.1 The risk of presenting for the investigation of infertility

The unadjusted relative risk of exposure to leatherwork in relation to presenting for the investigation of infertility was estimated by comparison of all the infertility study participants who were Leicestershire residents with the fathers of the control babies in the Leicestershire perinatal mortality survey. The use of the data for the infertility group relating to only the Leicestershire residents ensured that both the cases and controls were derived from the same geographical population base, thereby minimising the risk of geographical selection bias which could be a serious problem in an occupational study of this type. Confounder data were not available for the control population therefore only unadjusted odds ratios could be derived.

Men who were leatherworkers in their current or most recent job were only 1.10 times more likely to present for the investigation of infertility than non-leatherworkers. As

illustrated by the 95% confidence interval of 0.46 to 2.63, much uncertainty surrounded this estimate and the role of chance cannot be excluded. Confounding could also quite easily account for this finding. This result therefore suggests that leatherwork is not associated with a significant increase in the risk of presenting for the investigation of infertility.

5.4.2 The risk of oligozoospermia

Having presented with infertility, the analysis based on the infertility study participants alone enabled the calculation of adjusted odd ratios to estimate the relative risk of having oligozoospermia. Both the statistically and biologically derived analytical approaches produced an estimate which indicates that leatherwork is associated with a statistically non-significant elevated risk of oligozoospermia of only 20% (OR 1.20; 95%CI 0.43, 3.35). Clearly the role of chance cannot be excluded and the effects of residual confounding could quite easily explain such a small odds ratio. The confidence interval is very wide indicating that there is considerable uncertainty from this result as to the true relative risk.

The study had insufficient power to detect as statistically significant (at $P<0.05$) an effect as small as 1.20. In order to have had sufficient power (80%) to do this the study would have to have been 65 times larger (!). However, even having excluded the role of chance the concerns about the effects of residual confounding would have remained and an increased risk of 20%, even if real, is of limited clinical relevance.

The difficulty with the interpretation of findings which indicate no increase in risk associated with an exposure is that of determining the certainty of that conclusion. Whilst a

small relative risk of 1.20 could be explained by chance (if the confidence interval includes one) and residual confounding, when the confidence interval is wide, as in this case, the result is compatible with a high risk or a indeed a reduced risk. In this case the relative risk could easily be as high as 3.35 or as low as 0.43. The Bayesian method described by Burton [1994] allows the estimation of the subjective posterior probability (assuming a prior distribution which is uniform on the scale of the $\log_e$(odds)) that the true value of an odds ratio exceeds a threshold value of clinical relevance. In this instance the value of 2.0 was chosen as the relevant threshold since it was thought that a doubling in risk would be of clinical importance. It was estimated that there was only a 17% chance that the true odds ratio was 2.0 or greater. In other words whilst this possibility cannot be formally excluded, the odds in favour of a lesser effect are greater than 4:1 on.

So far in the discussion it has been assumed that an unbiased estimate of the relative risk was obtained. This assumption and its impact requires consideration. As discussed in section 5.2.6, it seems unlikely that misclassification of the exposure (leatherworker) had occurred and the study was designed to minimise the occurrence of information bias. However, it is quite possible that the biological and measurement variation inherent in semen analysis led to non-differential misclassification of the outcomes of interest (see section 5.2.5). This would have led to an underestimate of the true odds ratio. However, for the true odds ratio to have been 2.0 or higher given that the point estimate was 1.20, this misclassification would have had to have been substantial and considerably greater than that described by Tielemans *et al* [1996] who simulated probable real life scenarios.

In support of the odds ratio being unbiased and therefore a reflection of reality was the point estimate result from the multilevel modelling which showed that, having adjusted for

operations, social class and Leicestershire residence, leatherworkers experienced only a 6.0% reduction in sperm concentration compared to non-leatherworkers. A reduction which is not of clinical importance. Again considerable uncertainty surrounded this estimate (95%CI -44%, +55%), however the point estimated findings were consistent with the binary analysis results.

Again in support of the inferences so far are the findings relating to 'ever leatherwork'. The odds ratio for ever leatherwork was 0.88 (95% CI 0.48, 1.60) which suggests that there was a statistically non-significant 12% reduction in the risk of oligozoospermia associated with ever leatherwork. It was highly improbable (0.01%) that the true relative risk was 2.0 or greater. The multilevel modelling results were consistent with these findings.

Considered together all the results present a coherent picture which strongly suggests that there is little evidence from these data to support the hypothesis that leatherwork is a risk factor for the development of oligozoospermia.

5.4.3 The risk of low motility

The effect of exposure to leatherwork and the relative risk of presenting with low motility (50% or less motile sperm on all samples tested) was also examined. The adjusted odds ratio for low motility in relation to current (or most recent) work as a leatherworker was 0.46 (95%CI 0.17, 1.28). The point estimate result quite strongly suggests that leatherwork is not a risk factor for low sperm motility. The 95% confidence interval indicated that the result was not statistically significant and the probability estimate derived from Burton's method indicated that there was only a 0.2% chance that the true relative risk was 2.0 or greater.

The point estimate of 0.46 might appear at first sight to indicate that the exposure actually had a protective effect. However, care must be taken reaching such a conclusion since these results come entirely from a 'within-disease' group analysis. Thus, the results, rather than implying a 'protective' effect are more likely to be reflecting the fact that this exposure (leatherwork) is not as important as others in terms of this particular outcome (low motility).

The unadjusted median sperm motility results for the leatherworkers was 56% and for the non-leatherworkers was 40%. The multilevel modelling results indicated that leatherwork was associated with only a 0.8% increase in motility (95%CI -8.3%, +9.9%). The change indicated by the point estimate would have had little impact on the distribution of motility. However, given that the mode of the distribution of sperm motility was around the cut point for the binary division an increase as extreme as 9.9% (upper limit of the 95% confidence interval) would be consistent with a change in the distribution of the binary groups that could translate into an odds ratio result substantially less than one.

Considered together, although chance cannot be excluded, these results provide quite strong evidence that exposure to leatherwork in the current or most recent job is unlikely to be a risk factor for low motility. The findings from the ever leatherworker analysis also indicated no increase in risk of low motility associated with this exposure (OR 1.00; 95%CI 0.61, 1.65) and there was less than a 1% chance that the true odds ratio was 0.5 or less or 2.0 or greater. The multilevel modelling showed that ever leatherwork was associated with only a 1.3% reduction in motility (95%CI -6.6%, +3.9%).

In conclusion, these data provide quite strong evidence that exposure to leatherwork is unlikely to be a risk factor for low sperm motility.

5.4.4 The risk of high deformity

The results relating to high deformity presented an apparently mixed picture. The adjusted odds ratio for high deformity (70% or greater deformed sperm on all samples tested) associated with current (most recent) leatherwork was 1.74 (95%CI 0.39, 7.77). This suggests that leatherwork was associated with a 74% increase in the risk of high deformity. Whilst the result was not statistically significant there was quite a high (43%) chance that the true odds ratio was 2.0 or greater. However, given that the 95% confidence interval was so wide, there is actually little evidence either way.

As discussed for oligozoospermia, the two effects which might influence this result could be working in opposition. First, residual confounding must be considered as it could easily explain a relative risk as modest as 1.74. Second, the effects of probable misclassification of the outcome group must be considered. On the basis of the findings of Tielemans *et al* [1997] a change from 2.0 to 1.75 is of a magnitude that could be reasonably explained by the effects of outcome misclassification.

The point estimate from the multilevel modelling suggests that leatherwork (current or most recent) was associated with a 0.8% reduction in deformity (95%CI -9.4%, +7.7%). Given that the modal points of the distribution of deformity (about 38% for both groups) were well away from the binary cut-point, it is difficult to see how even the most extreme result (+7.7%) could result in the substantial shift in the deformity distribution for leatherworkers which would produce an odds ratio as high as 1.74. However, the width of the confidence interval around the point estimates point to a serious paucity of information underlying these comparisons and it would be unwise to draw strong conclusions from this apparent inconsistency which may simply be a consequence of random fluctuations in

small numbers.

The ever leatherworker results suggest that ever leatherwork is associated with a small and non-significant decrease in the risk of high deformity (OR 0.94; 95%CI 0.33, 2.66), with only a 7% chance that the true relative risk is 2.0 or greater.

From these data there is a modest amount of evidence to support the view that leatherwork may be a risk factor for high sperm deformity. However, much uncertainty surrounds this estimate and the possibility remains that this is simply a chance finding or an effect of residual confounding or indeed a mixture of the two.

5.4.5 Interpretation of the results in the light of evidence from the literature

From the study reported here there was little evidence that leatherwork leads specifically to oligozoospermia. There was quite strong evidence that leatherwork is not a risk factor for low sperm motility, and there was some evidence that it is a risk factor for high sperm deformity, although much uncertainty surrounds this particular finding. Furthermore, leatherwork does not appear to significantly increase the risk of presenting for the investigation of infertility.

Leatherwork, including tanning, has been extensively investigated in relation to the risk of cancer. There is clear evidence that leatherwork is associated with an increased risk of nasal and paranasal sinus cancer [Battista *et al*, 1995]; bladder cancer [Pirastus *et al*, 1996]; and lung cancer [Garabrant & Wegman, 1984; Coggon *et al*, 1986]. There is some evidence that it is associated with cancer of the larynx [Ahrens *et al*, 1991]; multiple myeloma [Walrath *et al*, 1987]; non-Hodgkin's lymphoma [Scherr *et al*, 1992]; leukaemia

[Fu *et al*, 1996]; cutaneous melanoma [Linet *et al*, 1995]; cancer of the pancreas [Edling *et al*, 1986; Mikoczy *et al*, 1996]; cancer of the stomach [Edling *et al*, 1986]; and soft tissue sarcoma [Mikoczy *et al*, 1994]. Some authors have also found an increased risk for multiple sclerosis [Amaducci *et al*, 1982] and motor neuron disease [Hawkes *et al*, 1989]; although others have not [Li *et al*, 1990]. These latter risks are thought to be mediated through exposure to benzene and other solvents. Solvent exposure is also thought to be the causal route to leukaemia in association with tanning [Fu *et al*, 1996]. Some of these cancer risks, in particular, cancer of the pancreas and stomach and soft tissue sarcoma , have been found in association with tanning rather than in manufacturing which uses leather [Edling *et al*, 1986].

Of particular note, from the reproductive point of view, is the increase in the risk of nonseminoma testicular cancer seen in leather industry workers in Ontario [Knight *et al*, 1996] and a cluster of testicular cancer cases among leatherworkers in New York [Marshall *et al*, 1990]. These observations were associated wholly with tanning for the latter and predominantly with tanning for the former. In this context it is interesting to note that only one of the men in the study presented here worked in a tannery. The remainder worked in manufacturing which used leather; predominantly the boot and shoe industry.

The other reproductive outcomes identified from the literature as being associated with leatherwork were the findings in relation to perinatal death described by Clarke & Mason [1985] and confirmed in two publications relating to one study by McDonald & McDonald [1986] and McDonald *et al* [1988]; the findings in relation to reduced fertility [Clarke & Mason, 1988; Sallmen *et al*, 1995]; spontaneous abortion [Agnesi *et al*, 1997]; preterm birth and or low birth weight [Sanjose *et al*, 1991]; and cleft palate [Bianchi *et al*, 1997].

However, all these findings relate to maternal exposure to leatherwork during pregnancy. No publications were found in the literature to indicate that leatherwork had previously been the subject of research in relation to male infertility.

5.5 WORK WITH SOLVENTS

Work with solvents was investigated as it was postulated at the outset that if there was an increased risk of oligozoospermia associated with leatherwork that this would be mediated through exposure to solvents. It is clear from a recent review by Scarpelli *et al* [1993] that work in the boot and shoe industry and leather goods industry is indeed associated with exposure to a wide range of organic solvents. For the purposes of the study presented here, work with solvents was defined *a priori* by review of the literature to define occupations known to be associated with solvent exposure (see appendix C). This process is likely to have led to exposure misclassification and this must be borne in mind in the interpretation of the findings.

5.5.1 The risk of presenting for the investigation of infertility

Men who worked with solvents in their current or most recent job were 1.73 times (95%CI 1.26, 2.38) more likely to present for the investigation of infertility than non-solvent workers. This result was statistically significant. However, given that confounder data were not available for the controls (from the perinatal mortality survey) this was an unadjusted estimate of relative risk and the role of confounding must be considered as a possible explanation for this apparently elevated risk. On the other hand, the misclassification inherent in the definition of the exposure group is likely to have led to an attenuation of the estimated relative risk towards the null.

The inference from this result is that work with solvents may be associated with a modest, but clinically relevant, increased risk of presenting for the investigation of infertility.

5.5.2. The risk of oligozoospermia

Both the unadjusted and adjusted analyses indicated that work with solvents (current or most recent) was associated with about a 30% increase in the risk of oligozoospermia (OR 1.31; 95%CI 0.90, 1.92). This result was not statistically significant and such a modest increase could be quite easily be explained by residual confounding. There was only a 1.5% chance that the true relative risk was 2.0 or greater.

Misclassification of both the exposure and outcome is likely to have occurred and both would tend to produce an odds ratio estimate nearer to the null than reality. However, the misclassification would have to have been very substantial to result in such a modest estimate if in reality the relative risk was as big as 2.0, although it is possible that this was so [Tielemans *et al*, 1997].

The results from the multilevel modelling are consistent with no increase in the risk of oligozoospermia. Only an 8% reduction in sperm concentration was found and even the most extreme reduction of 25%, which is consistent with this result (lower limit of the 95% confidence interval) would not be expected to lead to a substantial increase in the risk of oligozoospermia.

The elevated risk of oligozoospermia associated with ever solvent work was even more modest than the risk for current use. The estimate was 1.18 (95%CI 0.88, 1.60), it was highly improbable that the true relative risk was 2.0 or greater (0.03% chance) and the

percentage change in the sperm concentration was consistent with these findings.

Overall, there is little evidence from these data to support the hypothesis that work with solvents is a specific risk factor for oligozoospermia. Indeed these data strongly suggest that work with solvents, as defined in this study, is not a substantial risk factor for oligozoospermia in comparison to other types of infertility.

5.5.3 The risk of low motility

Solvent work (current or most recent) was associated with only a small increase in the risk of low motility (OR 1.15; 95%CI 0.82, 1.62). This result was not statistically significant and it was highly improbable (0.07% chance) that the true odds ratio was 2.0 or greater. Whilst misclassification of both exposure and outcome is likely to have occurred, it is unlikely that the effects were large enough to mask an important increase in risk such that the point estimate appeared as low as 1.15. Residual confounding is an obvious explanation for such a small increase in relative risk. The results from the multilevel modelling were consistent with these findings as were all the results from the analysis relating to the ever solvent workers.

In summary, there is little evidence from these data that solvent work is a risk factor for low sperm motility; indeed these data strongly suggest that work with solvents, as defined in this study, is not a risk factor for low sperm motility.

5.5.4 The risk of high deformity

Similarly, solvent work (current or most recent) was associated with only a small increase in the risk of high deformity (OR 1.13; 95%CI 0.59, 2.18). The role of chance was not

excluded, residual confounding is a likely explanation and it was improbable that the true relative risk was 2.0 or greater (5.1% chance). The multilevel modelling results in relation to current (most recent) solvent work and all the results relating to ever having worked with solvent were consistent with their being no substantial increase in the risk of high deformity in relation to solvent work. These data strongly suggest that work with solvents, as defined, is not a risk factor for high sperm deformity.

5.5.5 Interpretation of the results in light of the evidence from the literature

From the study reported here there was strong evidence to suggest that solvent work, as defined in this study, is not a risk factor for oligozoospermia, low motility or high deformity. However, the means by which the exposure groups were derived had potentially serious limitations and the possibility that misclassification of both exposure and outcome led to a false negative finding cannot be excluded. There was evidence that solvent work is a modest risk factor for presentation for the investigation of infertility, although confounding remains a possible explanation. If indeed solvent work is a risk factor for infertility it would appear to be working though mechanisms which are not restricted to effects on sperm concentration, motility and deformity†. Interestingly, if leatherwork *is* a risk factor for high sperm deformity, based on these findings, exposure to solvents is unlikely to be the explanation for this.

† If solvent work only operates through oligozoospermia, low sperm motility or high sperm deformity, then one would expect positive relative risks. If it only operates through other mechanisms then one would anticipate apparently protective relative risks in the 'within infertility presenter' analysis.

In 1994, Baker reviewed the extensive body of literature describing the adverse effects of occupational solvent exposure in relation to the central and peripheral nervous systems; its relationship with the occurrence of a variety of cancers; and the increased risk of renal, liver, pulmonary and cardio-vascular disease associated with occupational solvents [Baker, 1994]. A number of reproductive outcomes have also been investigated. Lindbolm *et al* [1990], Lipscomb *et al* [1991] and Agnesi *et al* [1997] all found an increased risk of spontaneous abortion associated with occupations with high solvent exposure. McDonald *et al* [1987] found an increased risk of urinary tract defects in the offspring of women exposed to solvents at work whilst pregnant. Tikkanen & Heinonen [1988] found a statistically non-significant increased risk of cardio-vascular anomalies, particularly ventricular septal defects, in babies exposed to occupational solvents *in utero*. Pregnancy related effects were described by Eskenazi *et al* [1988] who found an increased risk for both pre-eclampsia and pregnancy induced hypertension associated with solvent exposure during pregnancy. A significantly increased time-to-conception was found by Sallmen *et al* [1995] for women occupationally exposed to solvents, some of whom were leatherworkers in shoe factories.

Birth outcomes, in relation to paternal solvent exposure, have also been investigated to a limited extent. Daniell & Vaughan [1988] described a 1.6 fold increased risk for being low birth weight in the term infants of men who were vehicle body-shop workers and a 1.4 fold increased risk for painters. Brender & Suarez [1990] found that solvent exposed male workers were at a 2.53 fold increased risk of having a baby with anencephaly and the risk was greatest for painters (OR 3.43).

The glycol ethers are a group of solvents which have wide industrial and commercial applications. Their effects on the male reproductive system have been the subject of investigation. Animal work has investigated the effects on the male reproductive system of ethylene glycol monomethyl ether (EGME) and ethylene glycol monoethyl ether (EGEE) in multiple species. Wess [1992], in a review of these data concluded, that there is good evidence that EGME and EGEE and their acetates cause adverse effects. These included microscopic testicular lesions, testicular atrophy and infertility. Testicular histology was found to correlate closely with abnormal sperm morphology.

A small study of six EGME process workers compared clinical and semen findings to nine unexposed men [Cook *et al*, 1982]. However, not surprisingly this seriously under powered study failed to find any differences in the clinical, fertility or semen parameters investigated.

The effects of exposure to glycol ethers in paint were investigated by Welch *et al* [1988] in a study of shipyard painters. Of the eligible exposed painters, 50% (73) participated, although only 22% (40) of the non-exposed comparison group of clerks and marine draftsmen did likewise. The low participation was probably due to the requirement to provide a semen sample and underlines once again the difficulty in study recruitment when semen sample are required. In fact the authors concluded that non-response had not biased their findings. They found that the unadjusted mean sperm concentration was lower in the exposed group compared to the unexposed group, but not significantly so. The results for the motility and morphology showed no difference. However, having adjusted for cigarette smoking, the exposed group were 2.8 times more likely to have oligozoospermia than the unexposed, although this was still not statistically significant. In

addition 5% of the exposed group were azoospermic compared to none of the unexposed group and a general population expectation of 1%. Interestingly, however, the unexposed group were more likely to report fertility problems than the exposed group.

In order to investigate the reproductive effects of EGME, Ratcliffe *et al* [1989] investigated the semen findings in a group of men exposed whilst employed as metal casting process workers. Of the eligible exposed men 50% (37) agreed to participate and 26% (38) of the unexposed workers also participated. The mean sperm concentration was less in the exposed group compared to the unexposed group although not statistically or clinically so. The motility and deformity results were similar. The exposed group were 1.65 times (95%CI 0.43, 6.40) more likely to have oligozoospermia. This result was not statistically significant and was not adjusted for the effects of possible confounders.

Veulemans *et al* [1993] investigated 1019 cases with proven male infertility and 475 men from the same infertility clinic who were "diagnosed as normally fertile" and used as controls. Urine samples were tested for the presence of metabolites of ethylene glycol ethers and were detected in 39 of the cases and 6 of the controls. This represented an unadjusted odds ratio of 3.11 (95%CI 1.31, 7.40) which could be markedly confounded. The presence of the metabolites was associated with occupations with exposure to solvents, in particular paints.

In summary, three of these four studies [Welch *et al*, 1988; Ratcliffe *et al*, 1989; Veulemans *et al*, 1993] provided evidence, which taken together, is compatible with the animal evidence, although not compellingly so. One major problem was the small numbers in the two occupational studies and the small numbers of exposed cases and controls in

the clinic based study, leading to relatively low power in each. A further problem was the general failure to control for the effects of potential confounders.

The findings from the present study for exposure to solvent work are at variance with these general findings. However, this is not surprising, since two of the previous studies investigated occupations with high levels of exposure [Welch *et al*, 1988; Ratcliffe *et al*, 1989] and yet the effects found were very modest. In the study presented here a wide range of occupations with possible solvent exposure were investigated. This approach would inevitably have led to some misclassification together with a mixing of occupations with high and low levels of exposure. Thus, whilst a relationship between those occupations defined as work with solvents and abnormal semen finding was not found, the possibility remains that this was a false negative finding resulting from misclassification. The finding that solvent work may increase the risk of presenting with infertility would appear to support the possibility that the study simply failed to detect the mechanism by which it operated.

5.6 WELDING

The role of welding was investigated as part of the secondary aims of the study. There were two reasons why welding was of interest. First, in response to a hypothesis raised by Rachootin & Olsen [1983] and Mortenson [1988], Bonde and his co-workers carried out a series of studies investigating the reproductive effects of welding and found welding of mild steel to be a risk factor for infertility and altered semen parameters [Mortensen, 1988; Bonde *et al*, 1990; Bonde, 1990a; Bonde, 1990b; Bonde, 1990c; Bonde, 1993]. Bonde identified a series of limitations of the studies performed and concluded that future studies, preferably prospective cohort studies, were required to confirm (or refute) the findings

[Bonde, 1993]. The data set generated in the study reported here provided an opportunity to further investigate the effects of this exposure. Second, the results of testing of the primary hypothesis of this study were predominantly negative. In other words, the postulated elevated risk of oligozoospermia in relation to leatherwork was not demonstrated. Given this, reassurance as to the validity of the data set was sought and the testing of other hypotheses using the data set was one means of carrying out such a validation.

Since the study reported here was not designed primarily to investigate the effects of welding, it was not surprising that the analyses carried out relating to welding were under powered. Consequently the estimates of relative risk all had very wide confidence intervals and the results were not statistically significant, even when the magnitude of the relative risk estimates were of clinical importance.

5.6.1 The risk of presenting for the investigation of infertility

Compared to the perinatal mortality control population, the Leicestershire resident infertility group were nearly twice as likely to currently be employed as a welder (unadjusted OR 1.91; 95%CI 0.62, 5.88). This result was not statistically significant and given that confounder data were not available for the controls the effects of confounding were not adjusted for.

Misclassification of the exposure may have occurred. However, as discussed previously (section 5.2.6), welding is quite a clearly defined occupation and adding in the men who were not welders but who reported carrying out welding as part of their job, had no material effect on the adjusted odds ratios. It seems unlikely, therefore, that exposure

misclassification would have had a substantial effect in this situation.

The inference from this result is that being a welder is associated with a doubling in the risk of presenting for the investigation of infertility. However, the role of chance has not been excluded and the possibility remains that confounding at least partly explains this finding.

5.6.2 The risk of oligozoospermia

The adjusted odds ratios indicate that being a welder (current or most recent) was associated with about a 30% reduction in the risk of oligozoospermia (OR 0.72; 95%CI 0.15, 3.40). This result was not statistically significant and could be explained by residual confounding. There was only a 9% chance that the true relative risk was 2.0 or greater. The point estimate from the multilevel modelling was somewhat at variance with a protective relative risk. However, the confidence intervals were again so wide that a broad range of effects is consistent with all the results.

Ever welding was associated with a small increased risk of oligozoospermia (OR 1.17; 95%CI 0.51, 2.70). This was statistically not significant and residual confounding is a likely explanation for such a small odds ratio. There was only a 10% chance that the true relative risk was 2.0 or greater. The results from the multilevel modelling were consistent with the above binary results, although with a 36% reduction in sperm concentration associated with the exposure one might expect to see that translate into a risk of oligozoospermia higher than 1.17. Again, as discussed in section 5.4.3, this apparently protective effect is probably simply due to the nature of the 'within-disease' group analysis that was performed.

As discussed above, exposure misclassification is not likely to have contributed substantially although the possibility of outcome misclassification remains.

Overall, the findings relating to being a welder provide evidence that quite strongly suggests that being a welder is not a specific risk factor for oligozoospermia.

5.6.3 The risk of low motility

Both sets of results relating to current (most recent) and ever work as a welder suggest that there is a 30% to 40% reduction in the risk of low motility. Both sets of results could be explained by residual confounding and neither were statistically significant. There was only a 5% and 0.4% chance respectively, that the true relative risk was 2.0 or greater. The results from the multilevel modelling analysis were consistent with the odds ratio estimates of less than one.

In summary, these results provide strong evidence that being a welder is not a risk factor for low sperm motility.

5.6.4 The risk of high deformity

As there were no current (or most recent) welders with high sperm deformity the estimated odds ratio was zero with an upper 95% confidence limit of 4.86. This result was not very informative.

For ever welders the odds ratio associated with high deformity was 1.68 (95%CI 0.48, 5.81), with a 39% chance that the true relative risk was 2.0 or greater. Again the role of chance was not excluded and residual confounding was a possible explanation. At first

sight the findings from the multilevel modelling did not appear to be consistent with the binary analysis result point estimate. Being a welder was associated with a 0.9% *reduction* (95%CI -8.6%, +6.9%) in sperm deformity. However, the width of the confidence interval around the binary analysis estimate indicates that the results are consistent with a very wide range of values which include a value consistent with no effect.

In summary, there is some evidence of a modest increase in the risk of high deformity associated with ever being a welder although considerable uncertainty remains and the effect may be due to chance or residual confounding. There were too few data to be able to conclude anything about current (or most recent) work as a welder.

5.6.5 Interpretation of the results in light of the evidence from the literature

From the study reported here, there is evidence that being a welder is a modest risk factor for the presentation for the investigation of infertility, although chance and confounding remain possible explanations for this finding. The evidence strongly suggests that being a welder is not a risk factor for oligozoospermia or low sperm motility. In contrast there is some evidence of a modest increase in the risk of high deformity associated with ever being a welder although there is much uncertainty. It was not possible to comment on the risk for current welders. If indeed being a welder does increase the risk of infertility the mechanism for this action does not appear to be through the effects on sperm concentration or motility. There is a possibility that such an effect might be mediated by an effect on sperm deformity.

Welding is postulated to have an adverse effect on male fertility through a series of mechanisms which include welding-fume particulates and radiant heat [Bonde, 1993].

Exposure to welding fumes in humans is associated with high biological loads of chromium, manganese, nickel and lead, when lead coated steel is welded.

The findings of an increased risk of presenting for the investigation of infertility for welders, from this present study, is in keeping with the findings of Rachootin & Olsen [1983], Bonde [1990a] and Bonde *et al* [1990]. Rachootin & Olsen found a delayed time-to-conception associated with non-stainless steel welding (OR 1.4) but not with stainless steel welding (OR 1.0). Bonde *et al* [1990] found a significantly reduced fertility, measured as the probability of having a child the year after at least one year of welding exposure in Danish male metalworkers. In a separate study, Bonde [1990a] also found a statistically significant two fold increased risk of infertility in metalworkers exposed to welding compared to age-matched metalworkers who did not perform welding (adjusted OR 2.20; 95%CI 1.1, 4.6).

Rachootin & Olsen [1983] also found that welding stainless steel was associated with a reduction in sperm quality as defined by a binary division of the three parameters (sperm concentration, motility and deformity) together, *ie* poor sperm quality was defined as the presence of one abnormal parameter result.

In a study of welders, non-welding metalworkers and electricians, Bonde [1990b] found that sperm concentration was not reduced in either mild steel or stainless steel welders, although the total count per ejaculate was reduced. The proportion of abnormal forms was significantly increased and there was a decrease in sperm motility in mild steel welders but not stainless steel welders.

The findings from the present study concur with those of Bonde [1990b] with respect to sperm concentration and the possibility of an increased risk of sperm deformity. However, the findings relating to sperm motility are not in accord. In the present study welding was not a primary focus of the research at the outset, thus details as to the types of metals welded were not collected. It is therefore not possible to divide the welders on this basis as other authors have done. If the adverse effects of welding related primarily to mild steel welding and the welding carried out by the welders in the present study was a mixture, then any risk estimate would have been diluted and the odds ratios would have been attenuated and may this account for the discrepancies in the findings.

In summary, Bonde and other workers [Bonde, 1990a, 1990b, 1990c, 1993; Bonde *et al* 1990; Mortensen, 1988; Rachootin & Olsen, 1983] have found evidence to suggest that welding, particularly mild steel welding, is a hazard to male fertility. The findings from the present study add some weight to this proposition although the evidence cannot be viewed as definitive. As such, these findings provide some reassurance regarding the validity of the data set collected in the present study.

5.7 THE IMPLICATIONS OF THE FINDINGS

This study was designed to test the primary hypothesis that leatherwork is a risk factor for oligozoospermia. In attempting to test this hypothesis two different objectives were encompassed within the one study which was performed. The first attempted to determine if particular occupational exposures (leatherwork in particular) were associated with an increased risk of presenting for the investigation of infertility. The second sought to

investigate possible mechanisms through which exposure to particular occupations (particularly leatherwork) might adversely affect male fertility.

The design used to investigate the first question, used control data from the Leicestershire perinatal mortality survey. Whilst this was probably the best approach in the circumstances the limitations of the control data meant that confounding could not be controlled for. Thus, whilst these is some evidence from these data that work with solvents and being a welder are both risk factors for presenting for the investigation of infertility, confounding remains a possible explanation. Given the later findings the mechanism for such an effect, if in reality it exists, is unlikely to be a simple change in semen parameters and probably would operate through more global effects. The findings in relation to being a welder add to the evidence already available. The evidence relating to work with solvents is necessarily non-specific and the recommendation from this result is that further, more specific research is undertaken.

The design used to investigate the risks associated with oligozoospermia (low motility and high deformity) was based on an internal 'within-disease' group analysis and as such, apparently protective effects must be interpreted with caution. Rather than reflecting a protective effect they are more likely to reflect the fact that the exposure is not as important as others as a risk factor for the particular outcome. Although apparently protective effects could also be explained by protection against alternative mechanism. This would seem to be inherently less likely.

This part of the study provided results which suggest that there is little evidence in favour of the primary hypothesis. That is, leatherwork is unlikely to be a risk factor for the

development of oligozoospermia. There was also strong evidence that leatherwork is not a risk factor for low sperm motility. There was some, although not compelling evidence that leatherwork may be a risk factor for high sperm deformity. However, in the absence of an important increase in the risk of presenting with infertility, this evidence cannot be viewed as compelling.

Overall these findings should provide reassurance to the leatherworkers who use leather in manufacturing. As only one of the leatherworkers worked in a tannery these data provide no evidence as regards tanning. The only action recommended on the basis of these findings is to conduct further independent investigation of the potential sperm deformity relationship.

The proposition that any adverse effects of leatherwork would operate through exposure to solvents was also not borne out by the findings relating to solvent exposure. However, less reassurance can be taken from the results relating to work with solvents as the effects of exposure misclassification are likely to have been substantial and involved an admixture of occupations with high and low solvent exposure. Other authors have shown only modest effects on semen parameters with high levels of exposure, thus is it not surprising to see no apparent effect with such a heterogeneous exposure group. False negative findings from this study remain a strong possibility.

Although under powered to test the hypothesis, the findings relating to being a welder were generally in accord with published data. These findings added some weight to the proposition that being a welder is a risk factor for male infertility and suggest that this may operate through an increased risk of deformity. As such the findings provided some reassurance regarding the validity of the study data set.

Semen parameters provided an early measure of the possible impact of exposure on male fertility. The study identified a cohort of 1906 men who presented with their wives for the investigation of infertility. It is recommended that follow-up of this population is carried out. This would provide other informative measures of the effects of occupation on fertility.

SUMMARY AND CONCLUSIONS

6.1 IN SUMMARY

This study was designed to test the hypotheses that leatherwork is associated with male infertility, and that if so, this association is mediated though the development of oligozoospermia. The basis of any such associations was thought, *a priori*, to be with exposure to the solvents used in leatherwork. A secondary aim was to develop a data set upon which other independent hypotheses could be tested. For example, the hypothesis that male infertility is associated with being a welder was investigated.

An unmatched case control study was designed and conducted. Interviewer administered questionnaires collected occupational details and other information from 1906 men who presented with their partners as new referrals for the investigation of infertility in Leicestershire or at Kettering hospital between November 1988 and September 1992. This represented a response of 88.5%. Two principal sets of comparisons were made. First, the Leicestershire infertility presenters were compared as cases to 1013 fathers of control babies from the Leicestershire perinatal case control study. Second, a 'within infertility' analysis, restricted to the presenters with infertility, compared the characteristics of those men with oligozoospermia (cases) to those without (controls). Comparisons were also made for low sperm motility and high sperm deformity.

Leatherwork does not appear to significantly increase the risk of presenting for the investigation of infertility. Furthermore, there was little evidence that leatherwork leads specifically to oligozoospermia. There was quite strong evidence that leatherwork is not a risk factor for low sperm motility. There was some evidence that it may be a risk factor for

high sperm deformity. However, in the absence of an important increase in the risk of presenting with infertility, the evidence cannot be viewed as compelling. Furthermore, if leatherwork *is* a risk factor for high sperm deformity, exposure to solvents does not appear to be the explanation for this. Overall these findings should provide reassurance to the leatherworkers who use leather in manufacturing. Nothing can be concluded from these data about the risks related to tanning.

There was some evidence that work involving exposure to solvents is a modest risk factor for presentation with infertility. In contrast, there was strong evidence to suggest that solvent work, as defined in this study, is not a risk factor for oligozoospermia, low sperm motility or high sperm deformity. However, the possibility of both exposure and outcome misclassification remains; the possibility of a false negative finding cannot be excluded. If indeed solvent work is a risk factor for infertility it would appear to be working through mechanisms which are not restricted to effects on sperm concentration, motility or deformity.

The effect of being a welder was investigated as part of the secondary aim of the study. From these data there was some evidence that being a welder is a modest risk factor for infertility. The evidence strongly suggests that being a welder is not a risk factor for oligozoospermia or low sperm motility. In contrast there is evidence of a modest increase in the risk of high sperm deformity associated with ever being a welder. These findings add some weight to the proposition that being a welder is a risk factor for male infertility and suggest that this may operate through an increased risk of deformity. As such these findings also provide some reassurance regarding the validity of the study data set.

6.2 CONCLUSIONS

1. There is little evidence to support the joint hypotheses that leatherwork is associated either with an increased risk of presenting with infertility or with an elevated risk of oligozoospermia. Overall, these findings provide reassurance for leatherworkers who use leather in manufacturing.

2. There was a suggestion that leatherwork may be associated with high sperm deformity. However, the evidence supporting this suggestion is not compelling. Further investigation of this association is recommended.

3. Although solvent workers did appear to be at an increased risk of presenting with infertility, there was little evidence to suggest that exposure to work with solvents is a specific risk factor for oligozoospermia, low sperm motility or high sperm deformity. Less reassurance can be taken from these findings and further study is warranted.

4. The findings add weight to the existing evidence that being a welder is a risk factor for male infertility and suggests that this may operate through effects on sperm morphology.

5. Further long term follow-up of the cohort of men and their partners enrolled in this study is recommended. This would provide important additional information regarding the effect of occupation on fertility in both men and women.

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APPENDIX A

QUESTIONNAIRES

CONFIDENTIAL

University of Leicester,
Department of Community Health,
Clinical Sciences Building,
Leicester Royal Infirmary,
PO Box 65, LEICESTER LE2 7LX.

October 1988.

FERTILITY STUDY

ode number: ☐☐☐☐ ☐☐☐☐4

nterviewer: _____ ☐5

nsultant: _____ ☐☐7

nterpreter: ◯ No ☐8

◯ Yes: Name _____ ☐9

Language _____ ☐10

ace of interview:

◯ LRI clinic
◯ LGH clinic
◯ Other clinic _____
◯ Home
◯ Elsewhere _____ ☐☐12

te of interview: ___ / ___ / ___ ☐☐ ☐☐

ne at start of interview: _____ ☐☐18

it number: _____

lame: _____

ddress: _____

_____

_____ ☐☐☐☐ ☐☐☐25

ostcode: _____ ☐☐ ☐☐

.O.B. ___ / ___ / ___ ☐☐31

P: Name: _____

Address: _____ ☐☐☐34

tner's code: ☐☐☐☐ ☐☐☐☐38

1. How old are you ? _____ (yrs) ☐☐ 41

2. Where were you born ? _____ ☐☐ 42

3(a). What is your marital status ? _____ ☐ 43

(b). How long have you and your husband/partner been living together ? _____ (mths / yrs). ☐☐

Now I would like to ask you some questions about the work that you do:

4(a). Do you work ? ☐ 47

- ◯ Yes, working - Go to (b)
- ◯ No, unemployed - Go to (d)
- ◯ No, housewife - Go to (d)

(b). Do you have more than one job, for example two part-time jobs ? ☐ 48

- ◯ Yes, more than one job - Go to (c)
- ◯ No, only one job - Go to 5

(c). How many jobs do you have ? _____ ☐ 49

Which of the ____ (say correct number) jobs do you spend the most time doing ? _____ - Go to 5

d).Do you do any paid work in the home, for example are you an outworker ?

◯ Yes - Go to 5
◯ No - Go to (e)

☐ 50

e).Have you ever had a job outside the home or in the home ?

◯ Yes - Go to (f)
◯ No → Go to 6

☐ 51

f).How long ago did you last work ?_____(mths/yrs) - Go to 5

☐☐☐ 54

◯ Never been employed - Go to 6

. . . . . .

estion 5 is the employment question for the current job
those currently working and the last job for those who are
rrently unemployed.

a).What do you do for a living ? _____

☐☐☐.
☐☐ 59

_____

☐☐ 61

b).Does your job have a title or grade ? _____

☐ 62

_____

☐ 63

☐ 64

(c) ◯ Are you an employee ? - Go to (i)

◯ or are you, self-employed ? - Go to (ii)

(i) Employee - Are you an ?

◯ Apprentice or trainee
◯ Foreman/supervisor
◯ Manager
◯ None of these

How many people work in the place ?

◯ 1 - 2
◯ 3 - 24
◯ 25 - 99
◯ 100 - 999
◯ 1000 +

(ii) Self-employed - Do you employ other people ? If so how many ?

◯ No employees
◯ Employ 1 - 24
25 +

(d). Who do you work for ? _____

_____

_____

(e). Can you describe your job to me and explain exactly what you do and where you do it ? _____

_____

_____

(f). Do you mostly work:

◯ Regular days
◯ Shifts on days
◯ Shifts on nights
◯ Regular nights
◯ Rotating shifts
◯ Any other _____

◯ In one place
◯ Travelling around

☐ 65

☐ 66

(g).Is your workplace (tick one from each group)

○ Clean	○ Cold	○ Quiet	☐ 67
○ Dirty	○ Warm	○ Background noise	☐ 68
○ Very dirty	○ Hot	○ Noisy	☐ 69
	○ Very hot	○ Very noisy	
	○ Variable		

(h).Does your job involve any direct contact with any of the following:

(i) Y / N Solvents _____ ☐ 70

Y / N Glues/adhesives _____ ☐ 71

Y / N Cleaning agents _____ ☐ 72

Y / N Paint spraying _____ ☐ 73

Y / N Colour mixing solutions _____ ☐ 74

Y / N Any other unusual substances or chemicals _____ ☐ 75

_____

(ii) When at work do you regularly use a: (for each, if so how often ?) ☐☐☐☐ 4

Y / N Photocopier_____ ☐☐ 6

Y / N V.D.U._____ ☐☐ 8

Y / N Micro-wave oven_____ ☐☐ 10

Y / N An ultrasound device_____ ☐☐ 12

(iii)Y / N Do you work with or near any sort of radiation for example x-rays, radio-isotopes or ultra-violet ?_____ □□14

_____

(iv) Y / N Does your job involve doing any welding ?_____ □15

_____

(i).How long have you been doing this job for ?

_____(mths/yrs) □□□

(j).Have you always done the same job or have you had other jobs since leaving school ?

◯ Same - Go to (p)
◯ Other/s - Go to (k) □19

(k).How many other jobs have you had, that is jobs <u>which you have had for longer than 6 months</u> ? _____ □□21

- Go to additional long-term jobs sheets,
- After completing long-term jobs sheet go to (l).

(l).Have you ever had any jobs that have lasted more than one month but less than six months ?

◯ Yes - Go to (m)
◯ No - Go to (p) □22

m).How many of the jobs that lasted for between one and six months have you had ?

_____ - Go to (n) complete (n) then go to (p). ☐☐ 24

n).For each of the short-term jobs, that is those jobs which you had for between one and six months, can you tell me what the job was and roughly how long you were doing that job for ?

(i)Name of the job _____ ☐☐☐.

_____ ☐☐ 29

Duration _____ ☐ 30

(ii)Name of the job _____ ☐☐☐.

_____ ☐☐ 35

Duration _____ ☐ 36

iii)Name of the job _____ ☐☐☐.

_____ ☐☐ 41

Duration _____ ☐ 42

(iv)Name of the job _____ ☐☐☐.

_____ ☐☐ 47

Duration _____ ☐ 48

(v)Name of the job _____

_____

Duration _____

(vi))Name of the job _____

_____

Duration _____

(vii)Name of the job _____

_____

Duration _____

(viii)Name of the job _____

_____

Duration _____

(ix)Name of the job _____

_____

Duration _____

(x)Name of the job _____

_____

Duration _____

Note: if the interviewee has had more than 10 short-term jobs indicate the number in excess of 10 and then complete the rest on an additional short-term jobs sheet and fix in the back of the questionnaire.

Number in excess of 10: _____

(p). At the end of completing the employment section, if it has not already been mentioned:

Can I just check:

Have you ever worked in the boot, shoe or leather industry ?

◯ Yes - Complete sheet on this job, then go to 6

◯ No - Go to 6

---

ow I would like to ask you about hobbies or interests that ou might have:

Do you have any hobbies or interests outside work which involve the use of:

Y / N Solvents _____ ☐ 12

Y / N Glues/adhesives _____ ☐ 13

Y / N Cleaning agents _____ ☐ 14

Y / N Paint solutions _____ ☐ 15

Y / N Colour mixing solutions _____ ☐ 16

Y / N Any other unusual substances or chemicals _____ ☐ 17

_____

Do you do any welding as part of any of your hobbies ?

◯ Yes
◯ No ☐ 18

Do you have a microwave oven at home ?

◯ Yes
◯ No ☐ 19

I would now like to ask you some questions about your health.

7(a).Have you ever had any serious illnesses in the past ?

◯ Yes _____

◯ No _____

(b).In the past, have you ever had any investigations, examinations or treatment at a hospital, regarding having a baby ?

◯ Yes _____

◯ No _____

(d).Have you ever had any operations ?

◯ Yes _____

◯ No _____

(e).As a child did you ever have mumps ?

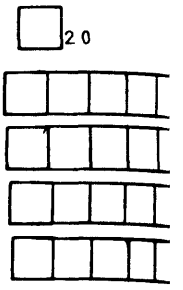
◯ Yes

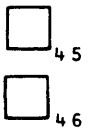
◯ No

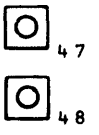
(f).Have you ever had to have any x-rays ? If 'yes', what did you have x-rayed ?

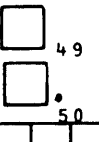
◯ Yes _____

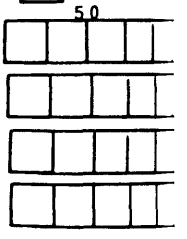
◯ No _____

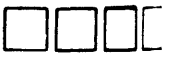


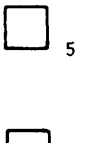












(g).Have you ever been in contact with any other sort of radiation ?

◯ Yes _____

◯ No _____

(a).Are you currently taking any medication or tablets prescribed by a doctor ? If 'yes' what are they ?

◯ Yes _____

◯ No _____

(b).Are you currently taking any medication or tablets that you have bought yourself ? If 'yes' what are they ?

◯ Yes _____

◯ No _____

(c).Have you <u>ever</u> taken any medication, tablets or treatment on a regular basis, that is for longer than a month ?

◯ Yes _____

◯ No _____

□□□
□□□
□□□
□□□

□□□

□ 27

Now I would like to ask you about some more general things.

9(a).Do you drink coffee ?

◯ Yes - Go to (b)

◯ No - Go to (c)

□ 28

(b).Do you drink ordinary or decaffeinated coffee ?

◯ Ordinary - How many cups do you drink on an average day ? _____ - Go to (c)

□□ 30

◯ Decaffeinated - Go to (c)

(c).Do you drink cola, or other drinks like it ?

◯ Yes - Go to (d)

□ 31

◯ No - Go to 10

(d).What sort of drinks like cola do you normally drink ?

_____

□□ 33

How many cans/bottles of ..... would you drink on average per week ?

_____

0. Do you drink alcohol ?

◯ Yes - Go through the following list:

◯ No - Can I just check, that is you never drink alcohol at all ?

☐ 34

o you drink ?	5+ days/ week	3-4 days/ week	1-2 days/ week	1-2 days/ month	Less than 1/mth	Never	Quantity consumed on a typical occasion ?
eer etc							☐☐☐ 37
pirits							☐☐☐ 40
ine							☐☐☐ 43
herry							☐☐☐ 46
thers							☐☐☐ 49

1(i). Have you ever smoked cigarettes, cigars or a pipe ?

◯ Yes - Go to (ii)

◯ No - Go to A

☐ 50

(ii) Do you smoke now ?

◯ Yes current - Go to C

◯ No ex-smoker - Go to B

☐ 51

A Non-smokers

Can I just check, have you ever smoked cigarettes, cigars or a pipe ?

◯ Yes ex-smoker - Go to B

◯ No never-smoker - Go to 12

☐ 52

B Ex-smoker

(iii)Can I just check, you have smoked in the past, but do not smoke now?

◯ Yes ex-smoker - Go to (iv)

◯ No - still smoking - Go to C

◯ No - never-smoker - Go to A

(iv)When did you start smoking ? _____ (age or year) ☐☐ 54

When did you give up smoking ? _____ (age or year) ☐☐☐ 57

What brand did you smoke most regularly ?

_____ ☐ 58

How many cigarettes (cigars or pipes) did you smoke per day, regularly ? _____ / day ☐☐ 60

- Go to 12

C Current smokers

When did you start smoking ? _____ (age or year) ☐☐ 62

What brand do you smoke ? _____ ☐ 63

How many cigarettes (cigars/ pipes) do you smoke per day normally ? _____ / day ☐☐ 65

- Go to 12

Finally, I would just like to ask you just a few questions about the reasons why you have come to the clinic

12. How long have you and your wife /partner been trying for a baby ? _____ (mths / yrs). ☐☐☐ 68

3(a)Have you and your wife ever had a child ?

◯ Yes - **END** ☐ 69

◯ No - Go to (b)

(b).Have you and your wife ever had a pregnancy ?

◯ Yes - **END** ☐ 70

◯ No - Go to (c)

(c).We are also interested in things which may have happened in the past, so I wonder if I could ask you if you have ever had a pregnancy in any of your previous relationships ?

◯ Yes - **END** ☐ 71

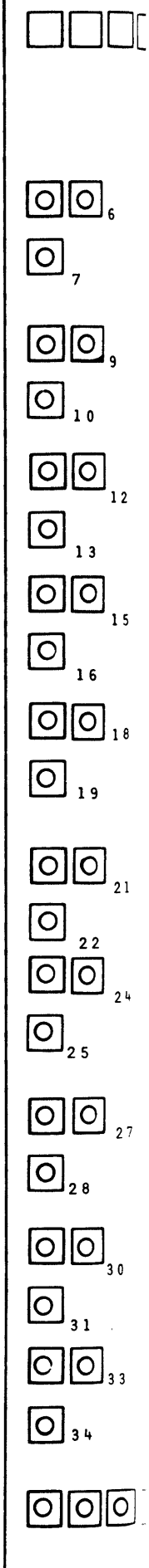
◯ No - **END**

☐☐ 73

☐ 74

THANK YOU VERY MUCH FOR YOU CO-OPERATION

Time at end of interview _____ ☐☐ 76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ADDITIONAL LONG-TERM JOBS SHEET 1.

or all previous long-term jobs, complete a separate sheet
or each job, in reverse chronological order of employment

or you last job
r
or your job before that:

. What was your job ? _____

_____

. Did you have a title or grade ? _____

_____

. Who did you work for ? _____

_____

_____

. Can you describe your job to me and explain exactly what you did and where you did it ? _____

_____

_____

. Did you mostly work:

- ◯ Regular days
- ◯ Shifts on days
- ◯ Shifts on nights
- ◯ Regular nights
- ◯ Rotating shifts
- ◯ Any other _____

- ◯ In one place
- ◯ Travelling around

Was your workplace (tick one from each group)

- ◯ Clean
- ◯ Dirty
- ◯ Very dirty

- ◯ Cold
- ◯ Warm
- ◯ Hot
- ◯ Very hot
- ◯ Variable

- ◯ Quiet
- ◯ Background noise
- ◯ Noisy
- ◯ Very noisy

□□□. 6
□□ 42
□ 43

□□□□

□ 5
□ 6

□ 7
□ 8
□ 9

G. Did your job involve any direct contact with any of the following:

(i) Y / N Solvents _____ ☐ 10

Y / N Glues/adhesives _____ ☐ 11

Y / N Cleaning agents _____ ☐ 12

Y / N Paint spraying _____ ☐ 13

Y / N Colour mixing solutions _____ ☐ 14

Y / N Any other unusual substances or chemicals _____ ☐ 15

_____

(ii) When at work did you regularly use a: (for each, if so how often ?)

Y / N Photocopier_____ ☐☐ 17

Y / N V.D.U._____ ☐☐ 19

Y / N Micro-wave oven_____ ☐☐ 23

Y / N An ultrasound device_____ ☐☐ 21

(iii) Y / N Did you work with or near any sort of radiation for example x-rays, radio-isotopes or ultra-violet ?_____ ☐☐ 25

_____

(iv) Y / N Did your job involve doing any welding ?_____ ☐ 26

_____

H. How long did you do this job for ?

_____(mths/yrs) ☐☐☐

I. Approximately when did you start it ? ___ / ___ (mth / yr)

NOW GO BACK TO PREVIOUS JOB AND COMPLETE THE NEXT SHEET

ADDITIONAL LONG-TERM JOBS SHEET 2.

A. What was your job ? _____

_____

□□□. □□ 48 □ 49

B. Did you have a title or grade ? _____

_____

C. Who did you work for ? _____

_____

_____

D. Can you describe your job to me and explain exactly what you did and where you did it ? _____

_____

_____

E. Did you mostly work:

- ○ Regular days
- ○ Shifts on days
- ○ Shifts on nights
- ○ Regular nights
- ○ Rotating shifts
- ○ Any other_____

- ○ In one place
- ○ Travelling around

□ 30 □ 31

F. Was your workplace (tick one from each group)

- ○ Clean
- ○ Dirty
- ○ Very dirty

- ○ Cold
- ○ Warm
- ○ Hot
- ○ Very hot
- ○ Variable

- ○ Quiet
- ○ Background noise
- ○ Noisy
- ○ Very noisy

□ 32 □ 33 □ 34

G. Did your job involve any direct contact with any of the following:

(i) Y / N Solvents _____ ☐ 35

Y / N Glues/adhesives _____ ☐ 36

Y / N Cleaning agents _____ ☐ 37

Y / N Paint spraying _____ ☐ 38

Y / N Colour mixing solutions _____ ☐ 39

Y / N Any other unusual substances or chemicals _____ ☐ 40

_____

(ii) When at work did you regularly use a: (for each, if so how often ?)

Y / N Photocopier_____ ☐☐ 42

Y / N V.D.U._____ ☐☐ 44

Y / N Micro-wave oven_____ ☐☐ 46

Y / N An ultrasound device_____ ☐☐ 48

(iii) Y / N Did you work with or near any sort of radiation for example x-rays, radio-isotopes or ultra-violet ?_____ ☐☐ 50

_____

(iv) Y / N Did your job involve doing any welding ?_____ ☐ 51

_____

H. How long did you do this job for ?

_____(mths/yrs) ☐☐☐

I. Approximately when did you start it ? ___ / ___ (mth / yr)

NOW GO BACK TO PREVIOUS JOB AND COMPLETE THE NEXT SHEET

ADDITIONAL LONG-TERM JOBS SHEET 3.

What was your job ? _____ ☐☐☐.

_____ ☐☐ 54

Did you have a title or grade ? _____ ☐ 55

_____

Who did you work for ? _____

_____

_____

Can you describe your job to me and explain exactly what you did and where you did it ? _____

_____

_____

Did you mostly work:

- ○ Regular days
- ○ Shifts on days
- ○ Shifts on nights
- ○ Regular nights
- ○ Rotating shifts
- ○ Any other _____

- ○ In one place
- ○ Travelling around

☐ 55

☐ 56

Was your workplace (tick one from each group)

- ○ Clean
- ○ Dirty
- ○ Very dirty

- ○ Cold
- ○ Warm
- ○ Hot
- ○ Very hot
- ○ Variable

- ○ Quiet
- ○ Background noise
- ○ Noisy
- ○ Very noisy

☐ 57

☐ 58

☐ 59

G. Did your job involve any direct contact with any of the following:

(i) Y / N Solvents _____ □60

Y / N Glues/adhesives _____ □61

Y / N Cleaning agents _____ □62

Y / N Paint spraying _____ □63

Y / N Colour mixing solutions _____ □64

Y / N Any other unusual substances or chemicals _____ □65

_____

(ii) When at work did you regularly use a: (for each, if so how often ?)

Y / N Photocopier_____ □□67

Y / N V.D.U._____ □□69

Y / N Micro-wave oven_____ □□71

Y / N An ultrasound device_____ □□73

(iii) Y / N Did you work with or near any sort of radiation for example x-rays, radio-isotopes or ultra-violet ?_____ □□75

_____

(iv) Y / N Did your job involve doing any welding ?_____ □76

_____

H. How long did you do this job for ?

_____(mths/yrs) □□□

I. Approximately when did you start it ? ___ / ___ (mth / yr)

NOW GO BACK TO PREVIOUS JOB AND COMPLETE THE NEXT SHEET

ADDITIONAL LONG-TERM JOBS SHEET 4.

□□□. 60 61

What was your job ? _____

_____

Did you have a title or grade ? _____

_____

Who did you work for ? _____

_____

_____

Can you describe your job to me and explain exactly what you did and where you did it ? _____

_____

_____

□□□□ B. 4

Did you mostly work:

- ○ Regular days
- ○ Shifts on days
- ○ Shifts on nights
- ○ Regular nights
- ○ Rotating shifts
- ○ Any other_____

- ○ In one place
- ○ Travelling around

□ 5
□ 6

Was your workplace (tick one from each group)

- ○ Clean
- ○ Dirty
- ○ Very dirty

- ○ Cold
- ○ Warm
- ○ Hot
- ○ Very hot
- ○ Variable

- ○ Quiet
- ○ Background noise
- ○ Noisy
- ○ Very noisy

□ 7
□ 8
□ 9

G. Did your job involve any direct contact with any of the following:

(i) Y / N Solvents _____ ☐ 10

Y / N Glues/adhesives _____ ☐ 11

Y / N Cleaning agents _____ ☐ 12

Y / N Paint spraying _____ ☐ 13

Y / N Colour mixing solutions _____ ☐ 14

Y / N Any other unusual substances or chemicals _____ ☐ 15

_____

(ii) When at work did you regularly use a: (for each, if so how often ?)

Y / N Photocopier_____ ☐☐ 17

Y / N V.D.U._____ ☐☐ 19

Y / N Micro-wave oven_____ ☐☐ 21

Y / N An ultrasound device_____ ☐☐ 23

(iii) Y / N Did you work with or near any sort of radiation for example x-rays, radio-isotopes or ultra-violet ?_____ ☐☐ 25

_____

(iv) Y / N Did your job involve doing any welding ?_____ ☐ 26

_____

H. How long did you do this job for ?

_____(mths/yrs) ☐☐☐

I. Approximately when did you start it ? ___ / ___ (mth / yr)

NOW GO BACK TO PREVIOUS JOB AND COMPLETE THE NEXT SHEET

ADDITIONAL LONG-TERM JOBS SHEET 5.

□□□.

What was your job ? _____

_____ □□ 66

Did you have a title or grade ? _____ □ 67

_____

Who did you work for ? _____

_____

_____

Can you describe your job to me and explain exactly what you did and where you did it ? _____

_____

_____

Did you mostly work:

- ○ Regular days
- ○ Shifts on days
- ○ Shifts on nights
- ○ Regular nights
- ○ Rotating shifts
- ○ Any other _____

- ○ In one place
- ○ Travelling around

□ 30

□ 31

Was your workplace (tick one from each group)

- ○ Clean
- ○ Dirty
- ○ Very dirty

- ○ Cold
- ○ Warm
- ○ Hot
- ○ Very hot
- ○ Variable

- ○ Quiet
- ○ Background noise
- ○ Noisy
- ○ Very noisy

□ 32

□ 33

□ 34

G. Did your job involve any direct contact with any of the following:

(i) Y / N Solvents _____ ☐ 35

Y / N Glues/adhesives _____ ☐ 36

Y / N Cleaning agents _____ ☐ 37

Y / N Paint spraying _____ ☐ 38

Y / N Colour mixing solutions _____ ☐ 39

Y / N Any other unusual substances or chemicals _____ ☐ 40

_____

(ii) When at work did you regularly use a: (for each, if so how often ?)

Y / N Photocopier_____ ☐☐ 4

Y / N V.D.U._____ ☐☐ 4

Y / N Micro-wave oven_____ ☐☐ 4

Y / N An ultrasound device_____ ☐☐ 4

(iii) Y / N Did you work with or near any sort of radiation for example x-rays, radio-isotopes or ultra-violet ?_____ ☐☐ 5

_____

(iv) Y / N Did your job involve doing any welding ?_____ ☐ 51

_____

H. How long did you do this job for ?

_____(mths/yrs) ☐☐[

I. Approximately when did you start it ? ___ / ___ (mth / yr)

NOW GO BACK TO PREVIOUS JOB AND COMPLETE THE NEXT SHEET

ADDITIONAL LONG-TERM JOBS SHEET 6.

What was your job ? _____ ☐☐☐.

_____ ☐☐ 72

Did you have a title or grade ? _____ ☐ 73

_____

Who did you work for ? _____

_____

_____

Can you describe your job to me and explain exactly what you did and where you did it ? _____

_____

_____

Did you mostly work:

- ◯ Regular days
- ◯ Shifts on days
- ◯ Shifts on nights
- ◯ Regular nights
- ◯ Rotating shifts
- ◯ Any other_____

- ◯ In one place
- ◯ Travelling around

☐ 55

☐ 56

Was your workplace (tick one from each group)

- ◯ Clean
- ◯ Dirty
- ◯ Very dirty

- ◯ Cold
- ◯ Warm
- ◯ Hot
- ◯ Very hot
- ◯ Variable

- ◯ Quiet
- ◯ Background noise
- ◯ Noisy
- ◯ Very noisy

☐ 57

☐ 58

☐ 59

G. Did your job involve any direct contact with any of the following:

(i) Y / N Solvents _____ ☐ 60

Y / N Glues/adhesives _____ ☐ 61

Y / N Cleaning agents _____ ☐ 62

Y / N Paint spraying _____ ☐ 63

Y / N Colour mixing solutions _____ ☐ 64

Y / N Any other unusual substances or chemicals _____ ☐ 65

_____

(ii) When at work did you regularly use a: (for each, if so how often ?)

Y / N Photocopier_____ ☐☐ 6

Y / N V.D.U._____ ☐☐ 6

Y / N Micro-wave oven_____ ☐☐ 71

Y / N An ultrasound device_____ ☐☐ 7

(iii) Y / N Did you work with or near any sort of radiation for example x-rays, radio-isotopes or ultra-violet ?_____ ☐☐ 7

_____

(iv) Y / N Did your job involve doing any welding ?_____ ☐ 76

_____

H. How long did you do this job for ?

_____(mths/yrs) ☐☐

I. Approximately when did you start it ? ___ / ___ (mth / yr)

NOW GO TO PREVIOUS JOB AND COMPLETE A LOOSE ADDITIONAL JOBS SHEET AND ATTACH IN THE BACK: NUMBER OF LOOSE SHEETS _____

NALYSIS 1:

ppearance _____

olume _____

resent / Absent

ount _____

otility _____

eformity _____

eucocytes _____

ndothelial _____

ed _____

NALYSIS 2:

ppearance _____

lume _____

esent / Absent

unt _____

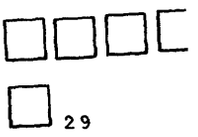
tility _____

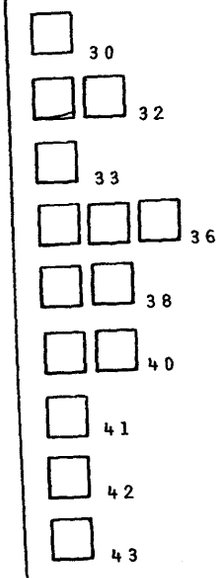
formity _____

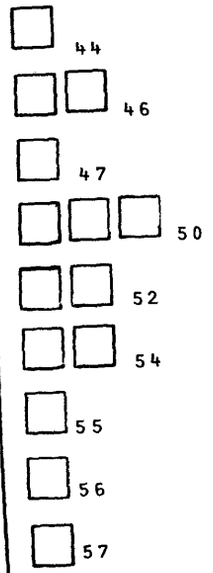
ucocytes _____

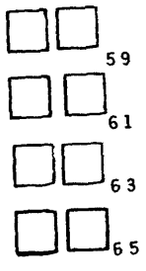
dothelial _____

d _____









CONFIDENTIAL

University of Leicester,
Department of Community Health,
Clinical Sciences Building,
Leicester Royal Infirmary,
PO Box 65, LEICESTER LE2 7LX.

October 1988.

FERTILITY STUDY

le number: ☐☐☐☐ ☐☐☐☐4

:erviewer: _____ ☐5

ısultant: _____ ☐☐7

:erpreter: ◯ No ☐8

◯ Yes: Name _____ ☐9

Language _____ ☐10

ıce of interview:

◯ LRI clinic
◯ LGH clinic
◯ Other clinic _____
◯ Home
◯ Elsewhere _____ ☐☐12

:e of interview: ___ / ___ / ___ ☐☐ ☐☐

ıe at start of interview: _____ ☐☐18

ıt number: _____

Name: _____

Address: _____

_____

_____ ☐☐☐☐ ☐☐☐25

Postcode: _____

).O.B. ___ / ___ / ___ ☐☐ ☐☐ ☐☐31

GP: Name: _____

Address: _____ ☐☐☐34

:tner's code: ☐☐☐☐ ☐☐☐☐38

1. How old are you ? _____ (yrs) ☐☐ 40

2. Where were you born ? _____ ☐☐ 42

3(a). What is your marital status ? _____ ☐ 43

(b). How long have you and your husband/partner been living together ? _____ (mths / yrs). ☐☐☐ 4

Now I would like to ask you some questions about the work that you do:

4(a). Do you work ?

◯ Yes, working - Go to (b) ☐ 47

◯ No, unemployed - Go to (d)
◯ No, housewife - Go to (d)

(b). Do you have more than one job, for example two part-time jobs ?

◯ Yes, more than one job - Go to (c) ☐ 48
◯ No, only one job - Go to 5

(c). How many jobs do you have ? _____ ☐ 49

Which of the ____ (say correct number) jobs do you spend the most time doing ? _____ - Go to 5

(d). Do you do any paid work in the home, for example are you an outworker ?

◯ Yes - Go to 5
◯ No - Go to (e)

☐ 50

(e). Have you <u>ever</u> had a job outside the home or in the home ?

◯ Yes - Go to (f)
◯ No → Go to 6

☐ 51

(f). How long ago did you last work ?_____(mths/yrs) - Go to 5

☐☐☐ 54

◯ Never been employed - Go to 6

. . . . . .

uestion 5 is the employment question for the current job
f those currently working and the last job for those who are
urrently unemployed.

(a). What do you do for a living ? _____

_____

☐☐☐.
☐☐ 59
☐☐ 61

(b). Does your job have a title or grade ? _____

_____

☐ 62
☐ 63
☐ 64

(c) ◯ Are you an employee ? - Go to (i)

◯ or are you, self-employed ? - Go to (ii)

(i) Employee - Are you an ?

◯ Apprentice or trainee
◯ Foreman/supervisor
◯ Manager
◯ None of these

(ii) Self-employed - Do you employ other people ? If so how many ?

◯ No employees
◯ Employ 1 - 24
25 +

How many people work in the place ?

◯ 1 - 2
◯ 3 - 24
◯ 25 - 99
◯ 100 - 999
◯ 1000 +

(d). Who do you work for ? _____

_____

_____

(e). Can you describe your job to me and explain exactly what you do and where you do it ? _____

_____

_____

(f). Do you mostly work:

◯ Regular days
◯ Shifts on days
◯ Shifts on nights
◯ Regular nights
◯ Rotating shifts
◯ Any other _____

◯ In one place
◯ Travelling around

☐ 65

☐ 66

(g).Is your workplace (tick one from each group)

◯ Clean	◯ Cold	◯ Quiet	☐ 67
◯ Dirty	◯ Warm	◯ Background noise	☐ 68
◯ Very dirty	◯ Hot	◯ Noisy	☐ 69
	◯ Very hot	◯ Very noisy	
	◯ Variable		

(h).Does your job involve any direct contact with any of the following:

(i) Y / N Solvents _____ ☐ 70

Y / N Glues/adhesives _____ ☐ 71

Y / N Cleaning agents _____ ☐ 72

Y / N Paint spraying _____ ☐ 73

Y / N Colour mixing solutions _____ ☐ 74

Y / N Any other unusual substances or chemicals _____ ☐ 75

_____

(ii) When at work do you regularly use a: (for each, if so how often ?) ☐☐☐☐

Y / N Photocopier_____ ☐☐ 6

Y / N V.D.U._____ ☐☐ 8

Y / N Micro-wave oven_____ ☐☐ 10

Y / N An ultrasound device_____ ☐☐ 12

(iii)Y / N Do you work with or near any sort of radiation for example x-rays, radio-isotopes or ultra-violet ?_____ □□ 14

(iv) Y / N Does your job involve doing any welding ?_____ □ 15

(i).How long have you been doing this job for ?

_____(mths/yrs) □□□ 1

(j).Have you always done the same job or have you had other jobs since leaving school ?

◯ Same - Go to (p)
◯ Other/s - Go to (k) □ 19

(k).How many other jobs have you had, that is jobs which you have had for longer than 6 months ? _____ □□ 21

- Go to additional long-term jobs sheets,
- After completing long-term jobs sheet go to (l).

(l).Have you ever had any jobs that have lasted more than one month but less than six months ?

◯ Yes - Go to (m)
◯ No - Go to (p) □ 22

m).How many of the jobs that lasted for between one and six months have you had ?

_____ - Go to (n) complete (n) then go to (p). □□ 24

n).For each of the short-term jobs, that is those jobs which you had for between one and six months, can you tell me what the job was and roughly how long you were doing that job for ?

(i)Name of the job _____ □□□.

_____ □□ 29

Duration _____ □ 30

(ii)Name of the job _____ □□□.

_____ □□ 35

Duration _____ □ 36

(iii)Name of the job _____ □□□.

_____ □□ 41

Duration _____ □ 42

(iv)Name of the job _____ □□□.

_____ □□ 47

Duration _____ □ 48

(v)Name of the job _____

_____

Duration _____

(vi))Name of the job _____

_____

Duration _____

(vii)Name of the job _____

_____

Duration _____

(viii)Name of the job _____

_____

Duration _____

(ix)Name of the job _____

_____

Duration _____

(x)Name of the job _____

_____

Duration _____

Note: if the interviewee has had more than 10 short-term jobs indicate the number in excess of 10 and then complete the rest on an additional short-term jobs sheet and fix in the back of the questionnaire.

Number in excess of 10: _____

(p). At the end of completing the employment section, if it has not already been mentioned:

Can I just check:

Have you ever worked in the boot, shoe or leather industry ?

◯ Yes - Complete sheet on this job, then go to 6

◯ No - Go to 6

---

ow I would like to ask you about hobbies or interests that ou might have:

. Do you have any hobbies or interests outside work which involve the use of:

Y / N Solvents _____ ☐ 12

Y / N Glues/adhesives _____ ☐ 13

Y / N Cleaning agents _____ ☐ 14

Y / N Paint solutions _____ ☐ 15

Y / N Colour mixing solutions _____ ☐ 16

Y / N Any other unusual substances or chemicals _____ ☐ 17

_____

Do you do any welding as part of any of your hobbies ?

◯ Yes
◯ No ☐ 18

Do you have a microwave oven at home ?

◯ Yes
◯ No ☐ 19

I would now like to ask you some questions about your health.

7(a). Have you ever had any serious illnesses in the past ? 20

◯ Yes _____

◯ No _____

(b). In the past, have you ever had any investigations, examinations or treatment at a hospital, regarding having a baby ? 45

◯ Yes _____

◯ No _____ 46

(c). Have you ever had pelvic inflammatory disease or any sort of pelvic infection ? 47

◯ Yes _____

◯ No _____ 48

(d). Have you ever had any operations ? 49

◯ Yes _____ 50

◯ No _____

(e). As a child did you ever have mumps ?

◯ Yes

◯ No

(f). Have you ever had to have any x-rays ? If 'yes', what did you have x-rayed ? 5

◯ Yes _____ 6

◯ No _____ 7

(g). Have you ever been in contact with any other sort of radiation ?

◯ Yes _____ ☐ 8

◯ No _____

(a). Are you currently taking any medication or tablets prescribed by a doctor ? If 'yes' what are they ?

◯ Yes _____ ☐ 9

◯ No _____

(b). Are you currently taking any medication or tablets that you have bought yourself ? If 'yes' what are they ?

◯ Yes _____ ☐ 34

◯ No _____

(c). Have you ever taken any medication, tablets or treatment on a regular basis, that is for longer than a month ?

◯ Yes _____ ☐ 59

◯ No _____

If not already mentioned in (c):

(d). Have you ever taken the oral contraceptive pill ?

◯ Yes - Go to (e)

◯ No - Go to 9 ☐ 11

(e).When did you start taking the pill ?

When did you stop taking the pill ?
(Start with the most recent pill history)

	1 most recent	2	3	4
Start				
Stop				

Can you remember the name of the pill that you took most recently ? _____

Now I would like to ask you about some more general things.

9(a).Do you drink coffee ?

◯ Yes - Go to (b)

◯ No - Go to (c)

(b).Do you drink ordinary or decaffeinated coffee ?

◯ Ordinary - How many cups do you drink on an average day ? _____ - Go to (c)

◯ Decaffeinated - Go to (c)

(c).Do you drink cola, or other drinks like it ?

◯ Yes - Go to (d)

◯ No - Go to 10

(d).What sort of drinks like cola do you normally drink ?

_____

How many cans/bottles of ..... would you drink on average per week ?

_____

10. Do you drink alcohol ?

◯ Yes - Go through the following list: ☐ 34

◯ No - Can I just check, that is you never drink alcohol at all ?

Do you drink ?	5+ days/ week	3-4 days/ week	1-2 days/ week	1-2 days/ month	Less than 1/mth	Never	Quantity consumed on a typical occasion ?
Beer etc							☐☐☐
Spirits							☐☐☐
Wine							☐☐☐
Sherry							☐☐☐
Others							☐☐☐

11(i). Have you ever smoked cigarettes, cigars or a pipe ?

◯ Yes - Go to (ii) ☐ 50

◯ No - Go to A

(ii) Do you smoke now ? ◯ Yes current - Go to C ☐ 51

◯ No ex-smoker - Go to B

A Non-smokers

Can I just check, have you ever smoked cigarettes, cigars or a pipe ?

◯ Yes ex-smoker - Go to B ☐ 52

◯ No never-smoker - Go to 12

B Ex-smoker

(iii) Can I just check, you have smoked in the past, but do not smoke now?

◯ Yes ex-smoker - Go to (iv)

◯ No - still smoking - Go to C

◯ No - never-smoker - Go to A

(iv) When did you start smoking ? _____ (age or year) ☐☐ 54

When did you give up smoking ? _____ (age or year) ☐☐☐

What brand did you smoke most regularly ?

_____ ☐ 58

How many cigarettes (cigars or pipes) did you smoke per day, regularly ? _____ / day ☐☐ 60

- Go to 12

C Current smokers

When did you start smoking ? _____ (age or year) ☐☐ 62

What brand do you smoke ? _____ ☐ 63

How many cigarettes (cigars/ pipes) do you smoke per day normally ? _____ / day ☐☐ 65

- Go to 12

Finally, I would just like to ask you just a few questions about the reasons why you have come to the clinic

12. How long have you and your husband/partner been trying for a baby ? _____ (mths / yrs). ☐☐☐

13(a)Have you ever had a child ?

◯ Yes - Go to (c) ☐ 69

◯ No - Go to (b)

(b).Have you ever been pregnant ?

◯ Yes - Go to (c) ☐ 70

◯ No - **END**

- **THANK YOU FOR YOUR CO-OPERATION.** ☒ 71

57

(c).How many times have you been pregnant ?

_____ - Now go to the pregnancy sheet and complete ☐☐ 73

it using questions (i) to (iii):

(i) When was your 1st (2nd / 3rd/ 4th .....) pregnancy ?

(ii) How many week or months did your 1st (2nd / 3rd / 4th.) pregnancy reach ?

(iii) What happened to your 1st (2nd / 3rd / 4th .....) pregnancy ?

- Now go to (d)

(d).Did you have your last pregnancy with your husband/ current partner ? Yes

No

- Now go to (e)

(e).Have you ever had a termination of pregnancy ? ◯ Yes ◯ No ☐ 74

THANK YOU VERY MUCH FOR YOU CO-OPERATION

6 Time at end of interview _____ ☐☐ 76

ADDITIONAL SHEET: PREGNANCY HISTORY

Pregnancy (year)	Gestation	Outcome

ADDITIONAL LONG-TERM JOBS SHEET 1.

For all previous long-term jobs, complete a separate sheet for each job, in reverse chronological order of employment

For you last job
or
For your job before that:

A. What was your job ? _____

_____

B. Did you have a title or grade ? _____

_____

C. Who did you work for ? _____

_____

_____

D. Can you describe your job to me and explain exactly what you did and where you did it ? _____

_____

_____

E. Did you mostly work:

- ◯ Regular days
- ◯ Shifts on days
- ◯ Shifts on nights
- ◯ Regular nights
- ◯ Rotating shifts
- ◯ Any other _____

- ◯ In one place
- ◯ Travelling around

F. Was your workplace (tick one from each group)

- ◯ Clean
- ◯ Dirty
- ◯ Very dirty

- ◯ Cold
- ◯ Warm
- ◯ Hot
- ◯ Very hot
- ◯ Variable

- ◯ Quiet
- ◯ Background noise
- ◯ Noisy
- ◯ Very noisy

6 □□□.
□□ 42
□ 43

□□□□

□ 5
□ 6

□ 7
□ 8
□ 9

G. Did your job involve any direct contact with any of the following:

(i) Y / N Solvents _____ ☐ 10

Y / N Glues/adhesives _____ ☐ 11

Y / N Cleaning agents _____ ☐ 12

Y / N Paint spraying _____ ☐ 13

Y / N Colour mixing solutions _____ ☐ 14

Y / N Any other unusual substances or chemicals _____ ☐ 15

_____

(ii) When at work did you regularly use a: (for each, if so how often ?)

Y / N Photocopier_____ ☐☐ 17

Y / N V.D.U._____ ☐☐ 19

Y / N Micro-wave oven_____ ☐☐ 21

Y / N An ultrasound device_____ ☐☐ 23

(iii) Y / N Did you work with or near any sort of radiation for example x-rays, radio-isotopes or ultra-violet ?_____ ☐☐ 25

_____

(iv) Y / N Did your job involve doing any welding ?_____ ☐ 26

_____

H. How long did you do this job for ?

_____(mths/yrs) ☐☐[

I. Approximately when did you start it ? ___ / ___ (mth / yr)

NOW GO BACK TO PREVIOUS JOB AND COMPLETE THE NEXT SHEET

ADDITIONAL LONG-TERM JOBS SHEET 2.

A. What was your job ? _____

_____

□□□.
□□ 48
□ 49

B. Did you have a title or grade ? _____

_____

C. Who did you work for ? _____

_____

_____

D. Can you describe your job to me and explain exactly what you did and where you did it ? _____

_____

_____

E. Did you mostly work:

- ◯ Regular days
- ◯ Shifts on days
- ◯ Shifts on nights
- ◯ Regular nights
- ◯ Rotating shifts
- ◯ Any other _____

- ◯ In one place
- ◯ Travelling around

□ 30
□ 31

F. Was your workplace (tick one from each group)

- ◯ Clean
- ◯ Dirty
- ◯ Very dirty

- ◯ Cold
- ◯ Warm
- ◯ Hot
- ◯ Very hot
- ◯ Variable

- ◯ Quiet
- ◯ Background noise
- ◯ Noisy
- ◯ Very noisy

□ 32
□ 33
□ 34

G. Did your job involve any direct contact with any of the following:

(i) Y / N Solvents _____ ☐ 35

Y / N Glues/adhesives _____ ☐ 36

Y / N Cleaning agents _____ ☐ 37

Y / N Paint spraying _____ ☐ 38

Y / N Colour mixing solutions _____ ☐ 39

Y / N Any other unusual substances or chemicals _____ ☐ 40

_____

(ii) When at work did you regularly use a: (for each, if so how often ?)

Y / N Photocopier_____ ☐☐ 42

Y / N V.D.U._____ ☐☐ 44

Y / N Micro-wave oven_____ ☐☐ 46

Y / N An ultrasound device_____ ☐☐ 48

(iii) Y / N Did you work with or near any sort of radiation for example x-rays, radio-isotopes or ultra-violet ?_____ ☐☐ 50

_____

(iv) Y / N Did your job involve doing any welding ?_____ ☐ 51

_____

H. How long did you do this job for ?

_____(mths/yrs) ☐☐☐

I. Approximately when did you start it ? ___ / ___ (mth / yr)

NOW GO BACK TO PREVIOUS JOB AND COMPLETE THE NEXT SHEET

ADDITIONAL LONG-TERM JOBS SHEET 3.

1. What was your job ? _____ ☐☐☐. ☐☐ 54 ☐ 55

_____

2. Did you have a title or grade ? _____

_____

3. Who did you work for ? _____

_____

_____

4. Can you describe your job to me and explain exactly what you did and where you did it ? _____

_____

_____

5. Did you mostly work: ☐ 55 ☐ 56

- ○ Regular days
- ○ Shifts on days
- ○ Shifts on nights
- ○ Regular nights
- ○ Rotating shifts
- ○ Any other_____

- ○ In one place
- ○ Travelling around

6. Was your workplace (tick one from each group) ☐ 57 ☐ 58 ☐ 59

- ○ Clean
- ○ Dirty
- ○ Very dirty

- ○ Cold
- ○ Warm
- ○ Hot
- ○ Very hot
- ○ Variable

- ○ Quiet
- ○ Background noise
- ○ Noisy
- ○ Very noisy

G. Did your job involve any direct contact with any of the following:

(i) Y / N Solvents _____ ☐60

Y / N Glues/adhesives _____ ☐61

Y / N Cleaning agents _____ ☐62

Y / N Paint spraying _____ ☐63

Y / N Colour mixing solutions _____ ☐64

Y / N Any other unusual substances or chemicals _____ ☐65

_____

(ii) When at work did you regularly use a: (for each, if so how often ?)

Y / N Photocopier_____ ☐☐67

Y / N V.D.U._____ ☐☐69

Y / N Micro-wave oven_____ ☐☐71

Y / N An ultrasound device_____ ☐☐73

(iii) Y / N Did you work with or near any sort of radiation for example x-rays, radio-isotopes or ultra-violet ?_____ ☐☐75

_____

(iv) Y / N Did your job involve doing any welding ?_____ ☐76

_____

H. How long did you do this job for ?

_____(mths/yrs) ☐☐

I. Approximately when did you start it ? ___ / ___ (mth / yr)

NOW GO BACK TO PREVIOUS JOB AND COMPLETE THE NEXT SHEET

ADDITIONAL LONG-TERM JOBS SHEET 4.

What was your job ? _____

_____

Did you have a title or grade ? _____

_____

Who did you work for ? _____

_____

_____

Can you describe your job to me and explain exactly what you did and where you did it ? _____

_____

_____

Did you mostly work:

- ○ Regular days
- ○ Shifts on days
- ○ Shifts on nights
- ○ Regular nights
- ○ Rotating shifts
- ○ Any other _____

- ○ In one place
- ○ Travelling around

Was your workplace (tick one from each group)

- ○ Clean
- ○ Dirty
- ○ Very dirty

- ○ Cold
- ○ Warm
- ○ Hot
- ○ Very hot
- ○ Variable

- ○ Quiet
- ○ Background noise
- ○ Noisy
- ○ Very noisy

□□□. 60 61

B. □□□□ 4

5 □

6 □

7 □

8 □

9 □

G. Did your job involve any direct contact with any of the following:

(i) Y / N Solvents _____ ☐ 10

Y / N Glues/adhesives _____ ☐ 11

Y / N Cleaning agents _____ ☐ 12

Y / N Paint spraying _____ ☐ 13

Y / N Colour mixing solutions _____ ☐ 14

Y / N Any other unusual substances or chemicals _____ ☐ 15

_____

(ii) When at work did you regularly use a: (for each, if so how often ?)

Y / N Photocopier_____ ☐☐ 1

Y / N V.D.U._____ ☐☐ 1

Y / N Micro-wave oven_____ ☐☐ 2

Y / N An ultrasound device_____ ☐☐ 2

(iii) Y / N Did you work with or near any sort of radiation for example x-rays, radio-isotopes or ultra-violet ?_____ ☐☐ 2

_____

(iv) Y / N Did your job involve doing any welding ?_____ ☐ 26

_____

H. How long did you do this job for ?

_____(mths/yrs) ☐☐☐

I. Approximately when did you start it ? ___ / ___ (mth / yr)

NOW GO BACK TO PREVIOUS JOB AND COMPLETE THE NEXT SHEET

ADDITIONAL LONG-TERM JOBS SHEET 5.

What was your job ? _____

_____

Did you have a title or grade ? _____

_____

Who did you work for ? _____

_____

_____

Can you describe your job to me and explain exactly what you did and where you did it ? _____

_____

_____

Did you mostly work:

- ○ Regular days
- ○ Shifts on days
- ○ Shifts on nights
- ○ Regular nights
- ○ Rotating shifts
- ○ Any other _____

- ○ In one place
- ○ Travelling around

Was your workplace (tick one from each group)

- ○ Clean
- ○ Dirty
- ○ Very dirty

- ○ Cold
- ○ Warm
- ○ Hot
- ○ Very hot
- ○ Variable

- ○ Quiet
- ○ Background noise
- ○ Noisy
- ○ Very noisy

□□□.
□□ 66
□ 67

□ 30
□ 31

□ 32
□ 33
□ 34

129

G. Did your job involve any direct contact with any of the following:

(i) Y / N Solvents _____ ☐ 35

Y / N Glues/adhesives _____ ☐ 36

Y / N Cleaning agents _____ ☐ 37

Y / N Paint spraying _____ ☐ 38

Y / N Colour mixing solutions _____ ☐ 39

Y / N Any other unusual substances or chemicals _____ ☐ 40

_____

(ii) When at work did you regularly use a: (for each, if so how often ?)

Y / N Photocopier_____ ☐☐ 42

Y / N V.D.U._____ ☐☐ 44

Y / N Micro-wave oven_____ ☐☐ 46

Y / N An ultrasound device_____ ☐☐ 48

(iii) Y / N Did you work with or near any sort of radiation for example x-rays, radio-isotopes or ultra-violet ?_____ ☐☐ 50

_____

(iv) Y / N Did your job involve doing any welding ?_____ ☐ 51

_____

H. How long did you do this job for ?

_____(mths/yrs) ☐☐☐

I. Approximately when did you start it ? ___ / ___ (mth / yr)

NOW GO BACK TO PREVIOUS JOB AND COMPLETE THE NEXT SHEET

ADDITIONAL LONG-TERM JOBS SHEET 6.

1. What was your job ? _____

_____

2. Did you have a title or grade ? _____

_____

3. Who did you work for ? _____

_____

_____

4. Can you describe your job to me and explain exactly what you did and where you did it ? _____

_____

_____

5. Did you mostly work:

- ○ Regular days
- ○ Shifts on days
- ○ Shifts on nights
- ○ Regular nights
- ○ Rotating shifts
- ○ Any other_____

- ○ In one place
- ○ Travelling around

6. Was your workplace (tick one from each group)

- ○ Clean
- ○ Dirty
- ○ Very dirty

- ○ Cold
- ○ Warm
- ○ Hot
- ○ Very hot
- ○ Variable

- ○ Quiet
- ○ Background noise
- ○ Noisy
- ○ Very noisy

54

□□□.
□□ 72
□ 73

□ 55
□ 56

□ 57
□ 58
□ 59

G. Did your job involve any direct contact with any of the following:

(i) Y / N Solvents _____ ☐ 60

Y / N Glues/adhesives _____ ☐ 61

Y / N Cleaning agents _____ ☐ 62

Y / N Paint spraying _____ ☐ 63

Y / N Colour mixing solutions _____ ☐ 64

Y / N Any other unusual substances or chemicals _____ ☐ 65

_____

(ii) When at work did you regularly use a: (for each, if so how often ?)

Y / N Photocopier_____ ☐☐

Y / N V.D.U._____ ☐☐

Y / N Micro-wave oven_____ ☐☐

Y / N An ultrasound device_____ ☐☐

(iii) Y / N Did you work with or near any sort of radiation for example x-rays, radio-isotopes or ultra-violet ?_____ ☐☐

_____

(iv) Y / N Did your job involve doing any welding ?_____ ☐ 76

_____

H. How long did you do this job for ?

_____(mths/yrs) ☐☐

I. Approximately when did you start it ? ___ / ___ (mth / yr)

NOW GO TO PREVIOUS JOB AND COMPLETE A LOOSE ADDITIONAL JOBS SHEET AND ATTACH IN THE BACK: NUMBER OF LOOSE SHEETS _____

ANALYSIS 1:

Appearance _____ 30

Volume _____ 32

Present / Absent 33

Count _____ 36

Motility _____ 38

Deformity _____ 40

Leucocytes _____ 41

Endothelial _____ 42

Red _____ 43

ANALYSIS 2:

Appearance _____ 44

Volume _____ 46

Present / Absent 47

Count _____ 50

Motility _____ 52

Deformity _____ 54

Leucocytes _____ 55

Endothelial _____ 56

Red _____ 57

59

61

63

65

APPENDIX B

DATA CODING MANUAL

INFERTILITY STUDY
CODING MANUAL

October 1988

Department of Community Health,
University of Leicester Medical School,
Clinical Sciences Building,
Leicester Royal Infirmary,
Leicester.

QUESTION NO	COL NO	INSTRUCTION	CODE

LEICESTERSHIRE FERTILITY STUDY 1988-93 CODING MATERIALS LIST

1. General coding manual - contains all the general codes.

2. Questions 7-8: Illnesses
   Operations
   Medications
   These were all coded with Read Codes.
   The specific Read Codes used are in the manual 'Useful Read Codes'

3. Page 1, General Practitioner codes - these were coded using the manual constructed from the FHSA list with GPs added as they moved into the area.

4. Occupation coding.

   Question 5 - present occupation and all past long-term occupations and short-term occupations were coded using the 1980 classification of occupations (OPCS) - the Green Book.

   In addition the present occupation was also coded using the 1980 classification of occupation (OPCS) - Blue Book - for comparison with the perinatal data set. These codes were coded in boxes 58-67 (card 7) on the last page of the questionnaire.

5. Post codes were coded using the appropriate Leicestershire and surrounding districts post code books.

JJK Feb 93.

QUESTION NO	COL NO	INSTRUCTION	CODE
CARD 1			
CODE NUMBER	1 - 4	Code number of the interviewee	****
		LRI men	0001 -
		LRI women	2500 -
		LGH men	5000 -
		LGH women	7500 -
		Kettering men	9000-9499
		Kettering women	9500-9998
INTERVIEWER	5	Anne Peel	1
		Lesley Parr	2
		Sue Pittam	3
		Mark Peel	4
		Elaine Metcalf	5
		Mary Muslin	6
		Linda Jones	7
CONSULTANT	6 - 7	Professor MacVicar	01
		Mr Naftalin	02
		Mr Lang	03
		Mr Davidson	04
		Mr Neuberg	05
		Mr Drife	06
		Mr Macafee	07
		Mr Stewart	08
		Mr Smith	09
		Mr Graham	10
		Mr Kirwan	11
		Mr Naftalin (Loughborough)	12
		Mr Graham (Hinckley)	13
		Mr Stewart (Melton)	14
		Mr Davidson (Harborough)	15
		Mr Smith (Oakham)	16
		Mr Roberts (B-O-T)	17
		Miss Laming	18
		Mr Newman	19
		Prof Simon (Notts)	20
		Mr Stewart (LGH special clinic)	21
		Mr Ireland	22
		Mr Dede-Chazal	23
		Mr Mayne	24
		Mr Al Azzawi	25
		Mr Anwar	26
		Mr Smart	27
		Missing	99
INTERPRETER (TRANSLATOR)	8	Yes	1
		No	2

QUESTION NO	COL NO	INSTRUCTION	CODE
		Missing	9
NAME	9	Friend/other	4
		Vinu Samani	1
		Not applicable	0
		Missing	9
		Gita Saha	2
		Relative	3
LANGUAGE	10	Hindi	1
		Gujarati	2
		Punjabi	3
		Urdu	4
		Bengali	5
		Arabic, Greek and others	6
		Not applicable	0
		Missing	9
PLACE OF INTERVIEW	11 - 12	LR1 Clinic	01
		LGH Clinic	02
		Other Clinic	
		- Loughborough	03
		- Hinckley	04
		- Harborough	05
		- Melton	06
		- Measham	07
		Home	08
		Others (telephone/wards)	09
		Maternity Hospital	10
		Kettering DGH	11
		Woodlands pat	12
		Missing	99
DATE OF INTERVIEW	13 - 18	Date as:	** ** **
		Day 01 - 31	
		Month 01 - 12	
		Year 88 - 93	
		Missing	99 99 99
POSTCODE	19 - 25	Postcode	****
		eg LE01 XXX	***
		to	
		LE15 XXX	
		(if unknown, check postcode book)	

QUESTION NO	COL NO	INSTRUCTION	CODE
DATE OF BIRTH	26 - 31	Date as: Day 01 - 31 Month 01 - 12 Year XX Missing	** ** ** 99 99 99
GENERAL PRACTITIONER	32 - 34	GP Code (as per code book) Missing Not registered with GP Armed forces GP	*** 999 000 762
PARTNERS CODE	35 - 38	Partners Code Number Partner declined interview	**** 8888
1. AGE	39 - 40	Age at last birthday in years Missing	** 99
2. PLACE OF BIRTH	41 - 42	UK Eire Europe East Europe N. America Canada S. America Africa Australia + Fiji West Indies India Pakistan China and Far East Bangladesh Middle East Missing	01 02 03 04 05 06 07 08 09 10 11 12 13 14 15 99
3a. MARITAL STATUS	43	Married Living together Not living together but in long term relationship Single Missing Not Applicable	1 2 3 4 9 0
3b. TIME TOGETHER	44 - 46	Time together in months eg. 001 to 240 (240 = 20 years) Missing Not applicable	*** 999 000

QUESTION NO	COL NO	INSTRUCTION	CODE
4a. WORKING?	47	Yes working	1
		No unemployed	2
		No housewife	3
		No student	4
		No retired	5
		Disabled	5
		Missing	9
4b. NUMBER OF JOBS	48	Yes more than one job	1
		No only one job	2
		Not applicable	0
		Missing	9
4c. NUMBER OF JOBS	49	Number of jobs	*
		Not applicable	0
		Missing	9
4d. HOMEWORK	50	Yes	1
		No	2
		Not applicable	0
		Missing	9
4e. EVER WORKED	51	Yes	1
		No	2
		Not applicable	0
		Missing	9
4f. WHEN LAST WORKED	52 - 54	Length of time since last worked in months	***
		Not applicable	000
		Missing	999
5a - e. OCCUPATIONAL CODING FROM INFORMATION FROM a - e		Refer to codes in classification of occupations 1980	
KEY OCCUPATION FOR STAT PURPOSES	55 - 59	KOS number	***. **
		eg. 136.01 to 136.12	
		Not applicable	000. 00

QUESTION NO	COL NO	INSTRUCTION	CODE
SOCIO ECONOMIC GROUP	60 - 61	SEG NUMBER 01 - 17 (ignore number after point ie 11.01 = 11)	
		Student	18
		Not applicable (never worked + armed forces)	00
SOCIAL CLASS	62	Class I	1
		II	2
		IIIN	3
		IIIM	4
		IV	5
		V	6
		Armed Forces / Students	7
		Housewife	8
		Not applicable	0
		Missing	9
MANUAL OR NON-MANUAL	63	Non-manual	1
		Manual	2
		Not applicable (and armed forces)	0
FOR FEMALE QUESTIONNAIRE: SOCIAL CLASS OF PARTNER	64	Social Class of Partner:	
		Class I	1
		II	2
		IIIN	3
		IIIM	4
		IV	5
		V	6
		Armed Forces / Students	7
		Missing	9
		Not applicable if not living with partner	0
		Partner not interviewed	8
FOR MALE QUESTIONNAIRE:	64	Code to zero	0

QUESTION NO	COL NO	INSTRUCTION	CODE
5f. WORKING ROTA	65	Regular days (includes part-time days)	1
		Shifts on days	2
		Shifts on nights	3
		Regular nights	4
		Rotating shifts	5
		Regular evenings	6
		Days and nights	7
		Not applicable	0
		Missing	9
		Other	8
5f. WORKING PLACE	66	In one place	1
		Travelling	2
		Variable	3
		Not applicable	0
		Missing	9
5g. WORK CONDITIONS (1)	67	Clean	1
		Dirty	2
		Very dirty	3
		Variable	4
		Not applicable	0
		Missing	9
5g. WORK CONDITIONS (2)	68	Cold	1
		Warm	2
		Hot	3
		Very hot	4
		Variable	5
		Not applicable	0
		Missing	9
5g. WORK CONDITIONS (3)	69	Quiet	1
		Background noise	2
		Noisy	3
		Very noisy	4
		Variable	5
		Not applicable	0
		Missing	9

QUESTION NO	COL NO	INSTRUCTION	CODE
5h. SOLVENT CONTACT	70	Yes contact	1
		No contact	2
GLUE CONTACT	71	Not applicable	0
		Missing	9
CLEANING AGENTS	72		
PAINT SPRAYING	73		
COLOUR MIXING	74		
OTHER	75		

QUESTION NO	COL NO	INSTRUCTION	CODE
CARD 2			
CODE NUMBER	1-4	CODE NUMBER	****
5h. continued			
PHOTOCOPIER	5	Yes uses	1
		Not used	2
		Not applicable	0
		Missing	9
5h. continued			
PHOTOCOPIER FREQUENCY	6	All day	1
		2-10 x day or more	2
		1 x day	3
		2-4 x week	4
		1 x week	5
		2 x month	6
		1 x month	7
		Less frequent	8
		Not applicable	0
		Missing	9
VDU USE	7	Yes uses	1
		Not used	2
		Not applicable	0
		Missing	9
VDU FREQUENCY USE	8	Hours per week:	
		Less than one	1
		1-5	2
		6-10	3
		11-15	4
		16-20	5
		21-25	6
		26-30	7
		31+	8
		Not applicable	0
		Missing	9

QUESTION NO	COL NO	INSTRUCTION	CODE
MICROWAVE	9	Use same coding as for: Photocopier use and	
MICROWAVE FREQUENCY USE	10	Photocopier frequency of use.	
ULTRASOUND	11		
ULTRASOUND FREQUENCY USE	12		
RADIATION	13	No contact	2
		Yes contact with x-ray	3
		Yes contact with isotopes	4
		Yes contact with U.V.	5
		Yes contact with multiple of the above	6
		Contact with others (CHECK BEFORE CODING)	7
		Not applicable	0
		Missing	9
5h. continued. RADIATION FREQUENCY CONTACT	14	All day	1
		2-10 x day or more	2
		1 x day	3
		2-3 x week	4
		1 x week	5
		2 x month	6
		1 x month	7
		Less frequent	8
		Not applicable	0
		Missing	9
5h. WELDING	15	Yes welding	1
		No welding	2
		Not applicable	0
		Missing	9
5i. DURATION OF WORK	16-18	Time in this job in months	***
		Not applicable	000
		Missing	999
		Less than 1 month	888
5j. SAME OR OTHER JOBS	19	Same job	1
		Other jobs	2
		Not applicable	0
		Missing	9

QUESTION NO	COL NO	INSTRUCTION	CODE
5k. NUMBER OF LONG TERM JOBS	20-21	Number of long term jobs	**
		Not applicable	00
		Too many / couldn't remember	98
		Missing	99
5l. SHORT TERM JOB?	22	Yes short term job	1
		No short term jobs	2
		Not applicable	0
		Missing	9
5m. NUMBER OF SHORT TERM JOBS	23-24	Number of short term jobs	**
		Not applicable	00
		Too many to remember	98
		Missing	99
5n. (i) KEY OCCUPATION FOR STAT PURPOSES	25-29	KOS number	***.
		eg. 136.01 to 136.12	**
		Not applicable	000.
			00
		Missing	999.
			99
		Uncodable	888.
			88
5n. continued MANUAL OR NON-MANUAL	30	Non-manual	1
		Manual	2
		Not applicable	0
		Missing	9
(ii) KOS AND - MANUAL/ (ix) NON-MANUAL	31-78	Convention as above for each job	

QUESTION NO	COL NO	INSTRUCTION	CODE
CARD 3			
CODE NUMBER	1-4	CODE NUMBER	****
5n. (x) KOS MANUAL/ NON-MANUAL	5-9 10	Convention as above for job (x)	
JOBS IN EXCESS OF 10	11	Number in excess of 10 jobs Not applicable Missing	* 0 9
6. HOBBIES			
SOLVENT CONTACT	12	Yes contact No contact Missing	1 2 9
GLUE CONTACT	13		
PAINT SPRAYING	15		
COLOUR MIXING	16		
OTHER	17		
WELDING	18	Yes No Missing	1 2 9
MICROWAVE OVEN	19	Yes No Missing	1 2 9
7a. SERIOUS ILLNESS	20	Yes ill in the past No illness Yes ill in the past and still ill Missing	1 2 3 9

QUESTION NO	COL NO	INSTRUCTION	CODE
WHAT SERIOUS ILLNESS?			
ILLNESS 1	21-26	Code each illness to the same convention	
ILLNESS 2	27-32	(Read codes)	
ILLNESS 3	33-38		
ILLNESS 4	39-44		
		Not applicable	All 0s
		Uncodable	All 8s
		Missing	All 9s
7b. INFERTILITY INVESTIGATED	45	Yes investigated	1
		No investigations	2
		Investigations by GP	3
		Investigated elsewhere as a private patient	4
		Missing	9

(NB If saw Mr Neuberg as PP and no investigations done, code = 2)
(Normal pregnancy visits and TOPs are not included here)

WHAT INVESTIGATIONS?	46	Blood tests/x-rays/scans/sperm count/HSG	1
		Laparoscopy +	2
		Laparoscopy and then treatment (incl ops)	3
		Treatment eg Clomid	4
		Sperm count/blood tests done by GP	5
		Investigations and treatment as PP	6
		Not applicable	0
		Missing	9
		Gone for investigations but none done	0

FOR FEMALE QUESTIONNAIRE:

7c. PELVIC INFLAMMATION	47	Yes	1
		No	2
		Missing	9
TREATMENT	48	Treated at home	1
		Admitted to hospital	2
		Not applicable	0
		Missing	9

FOR MALE QUESTIONNAIRE:

	47-48	Coded to zero	
7d. OPERATIONS	49	Yes	1
		No	2
		Missing	9

QUESTION NO	COL NO	INSTRUCTION	CODE
TYPE OF OPERATION	50	Abdominal operation/s / pelvic/genital	1
		Non-abdominal/s	2
		Abdominal AND non-abdominal	3
		Not applicable	0
		Missing	9
WHAT OPERATION?			
OPERATION 1	51-56	Code each operation by the same convention	
OPERATION 2	57-62	(Read codes)	
OPERATION 3	63-68		
OPERATION 4	69-74		
		Not applicable	All 0s
		Uncodable	All 8s
		Missing	All 9s

QUESTION NO	COL NO	INSTRUCTION	CODE
CARD 4			
CODE NUMBER	1-4	CODE NUMBER	****
7e. MUMPS	5	Yes had mumps	1
		No mumps	2
		Don't know	3
		Missing	9
7f. X-RAYS	6	Yes	1
		No	2
		Missing	9
X-RAYS OF WHAT?	7	Head/jaw/dental	1
		Limbs	2
		Chest	3
		Abdomen/pelvis	4
		Multiple including abdo/pelvis/back	5
		Multiple excluding abdo/pelvis/back	6
		Don't know what of	7
		Scans in pregnancy and not preg scans	8
		Not applicable	0
		Missing	9
7g. RADIATION CONTACT	8	Yes	1
		No	2
		Missing	9
8a. CURRENT MEDICATION	9	Yes	1
		No	2
		Missing	9
WHAT MEDICINE?		Code each drug to the same convention (Read codes)	
DRUG A	10-15		
DRUG B	16-21		
DRUG C	22-27		
DRUG D	28-33		
		Not applicable	All 0s
		Uncodable	All 8s
		Missing	All 9s
8b. BOUGHT MEDICINE	34	Yes	1
		No	2
		Missing	9

QUESTION NO	COL NO	INSTRUCTION	CODE
WHAT MEDICINE?		Code each drug to the same convention (Read codes)	
DRUG A	35-40		
DRUG B	41-46		
DRUG C	47-52		
DRUG D	53-58		
		Not applicable	All 0s
		Uncodable	All 8s
		Missing	All 9s
8c. PAST MEDICINE	59	Yes	1
		No	2
		Missing	9

(NB Do not include the oral contraceptive pill)
(If took medication in past and still taking, only need to be coded in current and not past medications)

WHAT MEDICINE?		Code each drug to the same convention (Read codes)	
DRUG A	60-65		
DRUG B	66-71		
DRUG C	72-77		
		Not applicable	All 0s
		Uncodable	All 8s
		Missing	All 9s
		Radiotherapy	888889
		Chemotherapy	888899

QUESTION NO	COL NO	INSTRUCTION	CODE
CARD 5			
CODE NUMBER	1-4	CODE NUMBER	****
DRUG D	5-10	Code drug to same convention (Read code)	
		Not applicable	All 0s
		Uncodable	All 8s
		Missing	All 9s
FOR FEMALE QUESTIONNAIRE:			
ORAL CONTRACEPTIVE	11	Yes taken	1
		No not taken	2
		Missing	9
FOR MALE QUESTIONNAIRE:			
ORAL	11	Coded to zero	
FOR FEMALE QUESTIONNAIRE:			
8e. PILL TAKING	12-14	Duration of use in months (1) (most recent)	***
DURATION	15-17	Duration of use in months (2)	***
	18-20	Duration of use in months (3)	***
	21-23	Duration of use in months (4)	***
		Not applicable	000
		Missing	999
		< 1 month	888
TIME SINCE LAST TOOK	24-26	Time since last stopped taking on last occasion in months	***
		Not applicable	000
		Missing	999
PILL LAST TOOK	27	Coded to pill list: (see appendix A)	
		Combined pill (21 day)	1
		Mini pill (28 day)	2
		Don't know	3
		Depo-provera	4
		Not applicable	0
		Missing	9
FOR MALE QUESTIONNAIRE:			
PILL	12-27	Coded to zero	0

QUESTION NO	COL NO	INSTRUCTION	CODE
9a. COFFEE DRINKING	28	Yes drink coffee	1
		No don't drink coffee	2
		Missing	9
9b. NUMBER OF CUPS OF ORDINARY COFFEE	29-30	Ignore decaffeinated drinkers	
		Number of cups ordinary per day	**
		(use maximum number mentioned)	
		Less than 1 day	88
		Not applicable	00
		Missing	99
9c. COLA	31	Yes drink cola	1
		No	2
		Missing	9
9d. CANS PER WEEK	32-33	Number of cans of cola per week	**
		Less than 1 / week	88
		Not applicable	00
		Missing	99

(NB 1 can = 330mls; therefor 1 litre = 3 cans)

10. ALCOHOL	34	Yes	1
		No	2
		Missing	9

(NB Alcohol - if stopped < 12 months age code up as prior consumption
-if stopped or altered 12 + months code up as zeros or as appropriate)

QUESTION NO	COL NO	INSTRUCTION	CODE

ALCOHOL CONVERSION FACTORS (These convert drinks to units of alcohol drunk per month)

DO YOU DRINK?	5+ days/ week	3-4 days/ week	1-2 days/ week	1-2 days/ month	Less than 1/ month	Never	Quantity consumed on a typical occasion?
BEER	x40	x32	x16	x4	x2	0	
SPIRITS	x20	x16	x8	x2	x1	0	
WINE	x20	x16	x8	x2	x1	0	
SHERRY	x20	x16	x8	x2	x1	0	
OTHERS	DEPENDS ON TYPE						

QUANTITY = 998 WHEN ALCOHOL IS DRUNK BUT THE AMOUNT IS MISSING
FOR BEER DRUNK IN HALF PINTS DIVIDE THE CONVERSION FACTOR BY TWO
FOR WINE - 1 BOTTLE = 6 GLASSES
FOR SHERRY - 1 BOTTLE = 15 UNITS
FOR SPIRITS - 1 BOTTLE = 30 UNITS
1 LITRE OF WINE = 8 GLASSES

BEER	35-37	Units converted as per factors	***
SPIRITS	38-40	Units converted as per factors	***
WINE	41-43	Units converted as per factors	***
SHERRY	44-46	Units converted as per factors	***
OTHERS	47-49	Units converted as per factors	***
		Alcohol drink but missing amount	998
		Not applicable	000
		Missing	999
11. SMOKING	50	Yes	1
		No	2
		Missing	9
SMOKE NOW	51	Yes current	1
		No ex-smoker	2
		Not applicable	0
		Missing	9

QUESTION NO		COL NO	INSTRUCTION	CODE
A.	NON-SMOKER	52	Yes ex-smoker	1
			No never smoked	2
			Not applicable	0
			Missing	9
B.	EX-SMOKER (IV) HISTORY	53-54	Duration of smoking in years	**
			Less than 1 year	88
			Not applicable	00
			Missing	99
	TIME SINCE STOPPED	55-77	Time since stopped smoking in months	***
			Not applicable	000
			Missing	999
	BRAND OF CIGARETTES	58	See appendix B:	
			Low tar	1
			Low to medium	2
			Medium tar	3
			High tar	4
			Insufficient info to code	4
			Respondent doesn't know	5
			Not yet analysed by gov chemist	7
			Cigars or pipe smoker	8
			Not applicable	0
			Missing	9

CIGARETTE EQUIVALENT CONVERSION FACTORS:

NUMBER OF SMALL CIGARS x 2 = NUMBER CIGARETTE EQUIVALENTS

NUMBER OF LARGE CIGARS x 5 = NUMBER CIGARETTE EQUIVALENTS

NUMBER OF OUNCES OF PIPE TOBACCO OR ROLL-OWN TOBACCO / WEEK x 4 = NUMBER CIGARETTE EQUIVALENTS DAILY

DAILY CONSUMPTION	59-60	Number of cigarettes or cigarette equivalents smoked daily	
		(use the maximum number mentioned)	**
		Less than 1/day	88
		Not applicable	00
		Missing	99

QUESTION NO	COL NO	INSTRUCTION	CODE
C. CURRENT SMOKERS			
DURATION OF SMOKING	61-62	Duration of smoking in years	**
		Less than 1 year	88
		Not applicable	00
		Missing	99
BRAND	63	See appendix B:	
		Low tar	1
		Low to medium	2
		Medium tar	3
		High tar	4
		Insufficient data to code	4
		Respondent doesn't know	5
		Not yet analysed by gov chemist	7
		Cigar or pipe smoker	8
		Not applicable	0
		Missing	9

CIGARETTE EQUIVALENT CONVERSION FACTORS:

NUMBER OF SMALL CIGARS x 2 = NUMBER CIGARETTE EQUIVALENTS

NUMBER OF LARGE CIGARS x 5 = NUMBER CIGARETTE EQUIVALENTS

NUMBER OF OUNCES OF PIPE TOBACCO OR ROLL-OWN TOBACCO / WEEK x 4 = NUMBER CIGARETTE EQUIVALENTS DAILY

DAILY CONSUMPTION	64-65	Number of cigarettes or cigarette equivalents smoked daily	
		(USE MAXIMUM NUMBER MENTIONED)	**
		Less than 1/day	88
		Not applicable	00
		Missing	99
12. TRYING FOR A BABY	66-68	Duration of trying for a baby in months	***
		Missing	999
		Husband doesn't think they are trying to have a baby	998

QUESTION NO	COL NO	INSTRUCTION	CODE
FOR FEMALE QUESTIONNAIRE:			
13a. HAD A CHILD	69	Using the information from questions (a) and (d):	
		Yes had a child, with current partner	1
		No child	2
		Yes had a child, with previous partner	3
		Missing	9
		Yes had child, ? father previous or current	4
13b.EVER PREGNANT	70	Using the information from questionnaire (b) and (d):	
		Yes pregnant with current partner	1
		No never pregnant	2
		Yes pregnant with past partner	3
		Not applicable	0
		Missing	9
		Pregnant but father not known to us	4
13b. continued			
BOX	71	Coded to zero	0
13c.NUMBER OF TIMES PREGNANT	72-73	Number of times	**
		Not applicable	00
		Missing	99
13e.TERMINATION OF PREGNANCY	74	Yes had TOP	1
		No TOP	2
		Not applicable	0
		Missing	9
(If had ectopic, this does <u>not</u> count as TOP)			
DURATION OF INTERVIEW	75-76	Duration of interview in minutes	**
		Missing	99
FOR MALE QUESTIONNAIRE:			
13a. HAD A CHILD	69	Yes had a child	1
		No child	2
		Missing	9
		Yes had a child but details of father missing (forgot to ask)	4
13b. PREGNANCY	70	Yes	1
		No	2
		Not applicable	0
		Missing	9
		Yes preg but details of father missing (as forgot to ask)	4

QUESTION NO	COL NO	INSTRUCTION	CODE
13c. PAST PREGNANCY	71	Yes	1
		No	2
		Not applicable	0
		Missing	9
BOXES	72-74	Coded to zero	0
DURATION OF INTERVIEW	75-76	Duration of interview in minutes	**
		Missing	99

QUESTION NO	COL NO	INSTRUCTION	CODE
CARD 6			
CODE NUMBER	1-4	CODE NUMBER	****
FOR FEMALE QUESTIONNAIRE:			
PREGNANCY 1			
GESTATION	5-6	Gestation in weeks	**
		If TOP	01
		Don't know	02
		Not applicable	00
		Missing	99
OUTCOME	7	Live born full-term	1
		Live born pre-term (37 weeks or less)	2
		Stillbirth	3
		Miscarriage	4
		Termination	5
		Ectopic pregnancy	6
		Not applicable	0
		Missing	9
PREGNANCY 2	8-10		
PREGNANCY 3	11-13		
PREGNANCY 4	14-16		
PREGNANCY 5	17-19		
PREGNANCY 6	20-22	Code all as for pregnancy 1	
PREGNANCY 7	23-25		
PREGNANCY 8	26-28		
PREGNANCY 9	29-31		
PREGNANCY 10	32-34		
TIME SINCE LAST PREGNANCY	35-37	Time since last pregnancy in months	***
		Not applicable	000
		Missing	999
FOR MALE QUESTIONNAIRE:			
CODE NUMBER	1-4	CODE NUMBER	****
BOXES	5-37	Coded to zero	

QUESTION NO	COL NO	INSTRUCTION	CODE

ADDITIONAL LONG TERM JOBS:

EACH ADDITIONAL LONG TERM JOB SHEET WILL BE CODED TOO THE SAME CONVENTION EVEN THOUGH THE COLUMN NUMBERS MAY VARY WITH EACH SHEET.

USING SHEET 1 AS AN EXAMPLE:

CARD 6

A-D		Refer to codes in Classification of Occupations 1980.	
KEY OCCUPATION FOR STATISTICAL PURPOSES	38-42	KOS number	***. **
		eg. 136.01 to 136.12	
		Not applicable	000. 00
MANUAL OR NON-MANUAL	43	Non-manual	1
		Manual	2
		Not applicable	0
		Missing	9

CARD A

CODE NUMBER	1-4	CODE NUMBER	****
E. WORKING ROTA	5	Regular days (includes part-time days)	1
		Shifts on days	2
		Shifts on nights	3
		Regular nights	4
		Rotating shifts	5
		Regular evenings	6
		Days and nights	7
		Not applicable	0
		Missing	9
E. WORKING PLACE	6	In one place	1
		Travelling	2
		Variable	3
		Not applicable	0
		Missing	9

QUESTION NO	COL NO	INSTRUCTION	CODE
F. WORK CONDITIONS (1)	7	Clean	1
		Dirty	2
		Very dirty	3
		Variable	4
		Not applicable	0
		Missing	9
WORK CONDITIONS (2)	8	Cold	1
		Warm	2
		Hot	3
		Very hot	4
		Variable	5
		Not applicable	0
		Missing	9
WORK CONDITIONS (3)	9	Quiet	1
		Background noise	2
		Noisy	3
		Very noisy	4
		Variable	5
		Not applicable	0
		Missing	9
Gi. SOLVENT CONTACT	10	Yes contact	1
		No contact	2
GLUE CONTACT	11	Not applicable	0
		Missing	9
CLEANING AGENTS	12		
PAINT SPRAYING	13		
COLOUR MIXING	14		
OTHER	15		
Gii. PHOTOCOPIER	16	Yes uses	1
		Not used	2
		Not applicable	0
		Missing	9

QUESTION NO	COL NO	INSTRUCTION	CODE
PHOTOCOPIER FREQUENCY	17	All day	1
		2-10 x day or more	2
		1 x day	3
		2-4 x week	4
		1 x week	5
		2 x month	6
		1 x month	7
		Less frequent	8
		Not applicable	0
		Missing	9
VDU USE	18	Yes uses	1
		Not used	2
		Not applicable	0
		Missing	9
VDU FREQUENCY USE	19	Hours per week:	
		Less than one	1
		1-5	2
		6-10	3
		11-15	4
		16-20	5
		21-25	6
		26-30	7
		31+	8
		Not applicable	0
		Missing	9
MICROWAVE	20	Use same coding for: Photocopier use and	
MICROWAVE FREQUENCY USE	21	Photocopier frequency of use.	
ULTRASOUND	22		
ULTRASOUND FREQUENCY USE	23		

QUESTION NO	COL NO	INSTRUCTION	CODE
iii. RADIATION	24	No contact	2
		Yes contact with x-ray	3
		Yes contact with isotopes	4
		Yes contact with U.V.	5
		Yes contact with multiple of the above	6
		Contact with others (CHECK BEFORE CODING)	7
		Not applicable	0
		Missing	9
RADIATION FREQUENCY	25	All day	1
		2-10 / day or more	2
		1 / day	3
		2-3 / week	4
		1 / week	5
		2 / month	6
		1 / month	7
		Less frequently	8
		Not applicable	0
		Missing	9
iv. WELDING	26	Yes welding	1
		No welding	2
		Not applicable	0
		Missing	9
H. DURATION OF WORK	27-29	Time in this job in months	***
		Not applicable	000
		Missing	999

COMPLETE ALL JOBS SHEETS WHEN REQUIRED TO THIS CONVENTION

IF THE PERSON DID NOT HAVE ANY OTHER JOBS CODE ALL TO ZEROS-
EXCEPT FOR CODE NUMBERS ON PAGES 17 AND 23 WHERE THE PERSONS CODE NUMBER SHOULD BE INSERTED

CARD 7

(FINAL PAGE)

CODE NUMBER	1-4	Code number	****

THERE IS NOW SPACE FOR CODING FOR ANY ADDITIONAL LONG TERM JOBS WHICH HAVE BEEN COMPLETED ON THE LOOSE SHEETS, ALTHOUGH THERE ARE NO BOXES IN THE BOOKLET. THE CODING SHOULD BE COMPLETED ON THE LOOSE SHEETS.

IF THE PERSON DID NOT HAVE ANY SUCH SHEETS THE FOLLOWING INSTRUCTIONS CAN BE IGNORED AND GO TO THE CODING INSTRUCTIONS FOR THE SEMEN ANALYSIS.

THE CODING CONVENTION ALLOWS FOR CODING OF 4 FURTHER JOBS ON LOOSE SHEETS:

JOB 7 KEY OCCUP FOR STAT PURPOSES	5-9	Using the classification of occupation 1980 code KOS number eg. 131.01 to 131.12 Not applicable Missing	***. ** 000. 00 999. 99
MANUAL OR NON-MANUAL	10	Non-manual Manual Not applicable Missing	1 2 0 9
JOB 8	11-16	Code jobs 8-10 with same convention as for job 7	
JOB 9	17-22		
JOB 10	23-28		
JOBS IN EXCESS OF 10	29	Number of jobs in excess of 10 Not applicable Missing	* 0 9

QUESTION NO	COL NO	INSTRUCTION	CODE
ANALYSIS 1 (ANALYSIS 2 CODED IN BOXES 44-57 - SAME CODING AS FOR ANALYSIS 1)			
APPEARANCE	30	Clear / normal	1
		Cloudy / abnormal / viscous	2
		Missing	9
VOLUME	31-32	Volume in mls (ignore decimal point)	
		eg 1.0 -9.5 = 10 - 95	**
		10.0 + mls	98
		Missing	99
SPERM PRESENT/ ABSENT	33	Present	1
		Absent	2
		Missing	9
CONCENTRATION IN MILLIONS/ ML	34-36	Concentration in millions/ml	***
		eg 001 - 500	
		000	000
		Less than 001	998
		Missing	999
% MOTILITY	37-38	% motility	**
		eg 00 - 98	
		100%	98
		Missing	99
%DEFORMITY	39-40	%Deformity	**
		eg 00 - 98	
		100%	98
		Missing	99
LEUCOCYTES	41	1 + / present	1
		2 +	2
		3 +	3
		More	4
		None	5
		Missing	9
ENDOTHELIAL	42	1 + / present	1
		2 +	2
		3 +	3
		More	4
		None	5
		Missing	9

QUESTION NO	COL NO	INSTRUCTION	CODE
RED CELLS	43	1 + / present	1
		2 +	2
		3 +	3
		More	4
		None	5
		Missing	9

LEAVE BOXES 58 TO 65 BLANK

QUESTION NO	COL NO	INSTRUCTION	CODE
CARD 7 CONTD.			
CODES RELATING TO THE CLASSIFICATION OF CURRENT OCCUPATION USING THE 1970 CLASSIFICATION OF OCCUPATIONS:			
CURRENT OCCUPATION/ MOST RECENT OCCUPATION	58-60	Occupation code	001-223
		Unemployed always	333
		Housewife	444
		Student	555
		Uncodable	888
		Missing	999
INDUSTRY OF CURRENT OCCUPATION	61-63	Industry code	001-906
		Unemployed - not applicable	000
		Housewife - not applicable	000
		Student - not applicable	000
		Unclassifiable	998
		Missing	999
SOCIAL CLASS	64	Social Class I	1
		II	2
		IIIN	3
		IIIM	4
		IV	5
		V	6
		Armed forces/student	7
		Housewife	8
		Not applicable	0
		Missing	9
SOCIO-ECONOMIC GROUP	65-66	SEG classification from 1970 Class	1-15
		Armed forces	16
		Inadequately described	17
		Students	18
		Housewife	19
		Not applicable	00
		Missing	99

QUESTION NO	COL NO	INSTRUCTION		CODE
FEMALE QUESTIONNAIRES ONLY:				
SOCIAL CLASS OF PARTNER	67	Social Class	I	1
			II	2
			IIIN	3
			IIIM	4
			IV	5
			V	6
		Armed forces/student		7
		Partner not interviewed		8
		Not applicable, if not living with partner		0
		Missing		9
MALE QUESTIONNAIRES ONLY:				
BOX	67	Code to zero		0

APPENDIX C

I. CODES DEFINING LEATHERWORK USING THE 1970 OPCS CLASSIFICATION OF OCCUPATION [OPCS, 1970]

061 Shoemakers and shoe repairers
062 Cutters, lasters, sewers, footwear and related workers
063 Leather products makers nec*

II. CODES DEFINING WORK WITH SOLVENTS USING THE 1970 OPCS CLASSIFICATION OF OCCUPATION [OPCS, 1970]

012 Chemical production process workers nec*
061 Shoemakers and shoe repairers
062 Cutters, lasters, sewers, footwear and related workers
063 Leather products makers nec*
070 Dyers of textiles
071 Textile fabrics and related products makers and examiners nec*
087 Printers (so described)
088 Printing workers nec*
089 Workers in rubber
090 Workers in plastics
099 Aerographers, paint sprayers
100 Painters, decorators nec*
101 Coach painters (so described)
204 Chemists†
219 Laboratory assistants, technicians

III. CODES DEFINING LEATHERWORK USING THE 1980 OPCS CLASSIFICATION OF OCCUPATION [OPCS, 1970]

08401 Foremen: Tannery production workers
08402 Foremen: Shoe repairers
08403 Foremen: Leather cutters and sewers, footwear lasters, makers, finishers
08404 Foremen: Other making and repairing, leather
08501 Workers: Tannery production workers
08502 Workers: Shoe repairers
08503 Workers: Leather cutters and sewers, footwear lasters, makers, finishers
10707 All others in making and repairing leather

IV. CODES DEFINING WORK WITH SOLVENTS USING THE 1980 OPCS CLASSIFICATION OF OCCUPATION [OPCS, 1980]

08401 Foremen: Tannery production workers
08402 Foremen: Shoe repairers
08403 Foremen: Leather cutters and sewers, footwear lasters, makers, finishers
08404 Foremen: Other making and repairing, leather
08501 Workers: Tannery production workers
08502 Workers: Shoe repairers
08503 Workers: Leather cutters and sewers, footwear lasters, makers, finishers
10707 All others in making and repairing leather
16002 General labourers: Chemical and allied trades
15902 Foremen: Chemical and allied trades
13801 Laboratory assistants
13804 Inspectors, viewers, examiners: Rubber goods
13805 Inspectors, viewers, examiners: Plastic goods
13807 Inspectors, sorters in paper production, processing and printing
13808 Assemblers in paper production, processing and printing
13809 Assemblers (plastic goods)
13604 Foremen: Rubber goods
13605 Foremen: Plastic goods
13405 Foremen: Assemblers - plastic goods
13404 Foremen: Assemblers - paper production, processing and printing
13301 Painters, decorators, french polishers - pottery decorators
13302 Painters, decorators, french polishers - coach painters (so described)
13303 Painters, decorators, french polishers - other paint sprayers
13304 Painters, decorators, french polishers - painters and decorators nec*, french polishers
13201 Foremen: Pottery decorators
13202 Foremen: Coach painters (so described)
13203 Foremen: Other paint sprayers
13204 Foremen: Painters and decorators nec*, french polishers
10709 All others in making and repairing - paper goods and printing
10710 All others in making and repairing - rubber
10711 All others in making and repairing - plastic
10001 Painting workers, screen and block printers - compositors
10002 Painting workers, screen and block printers - electrotypers, stereotypers, printing plate and cylinder preparers
10003 Painting workers, screen and block printers - printing machine minders and assistants
10004 Painting workers, screen and block printers - screen and block printers
10005 Painting workers, screen and block printers - printers (so described)
09901 Foremen - printing - compositors
09902 Foremen - printing - electrotypers, stereotypers, printing plate and cylinder preparers
09903 Foremen - printing - printing machine minders and assistants
09904 Foremen - printing - screen and block printers
09905 Foremen - printing - printers (so described)
09701 Rubber process workers, moulding machine operators, tyre builders

09702 Calender and extruding machine operators, moulders (plastics)
09509 Foremen - rubber
09510 Foremen - plastics
09504 Foremen - rubber process workers, moulding machine operators, tyre builders
09305 Foremen - other making and repairing, paper goods and printing
08900 Chemical, gas and petroleum process plant operators
08800 Foremen - chemical processing
08707 Textile workers - bleachers, dyers, finishers
08607 Foremen - bleachers, dyers, finishers
07503 Launderers, dry cleaners, pressers
05503 Sales assistants - petrol pump, forecourt attendants
05402 Sales supervisor - petrol pump, forecourt attendants
02801 Chemical engineers
02402 Chemical scientists

V. CODES DEFINING WORK IN THE LEATHER INDUSTRY USING THE 1970 OPCS CLASSIFICATION OF OCCUPATION [OPCS, 1970]

431 Leather (tanning and dressing) and fellmongery
432 Leather goods
450 Footwear
495 Repair of boots and shoes

*nec - not elsewhere classified
†Chemists not pharmacists

APPENDIX D

I. DISEASES WHICH MAY POTENTIALLY IMPAIR MALE FERTILITY

This is the list of the subset of diseases reported at interview, with their associated Read codes, which may potentially impair male fertility either by virtue of the pathogenesis of the disease or the treatment:

Disease	Read code
Cancer colon	1A54X4
Cancer of testicle	1W+1G5
Chronic renal failure	86884F
Diabetes	298012
Non-Hodgkins and Hodgkins lymphoma	1X778-
Hyperprolactinaemia	298+-3
Klinefelters Syndrome	999JJK
Orchitis	875F5+
Hypothyroidism	2919W7
Multiple sclerosis	518804

II. OPERATIONS WHICH MAY POTENTIALLY IMPAIR MALE FERTILITY

This is the list of the subset of operations reported at interview, with their associated Read codes, which may potentially impair male fertility either by virtue of the pathogenesis of the disease for which the operation was performed or the actual operation itself:

Operation	Read code
Epididymal cyst	467757
Testicular adenoma	1W+1G4
Testicular torsion	46714+
Prostatectomy	453+70
Bladder lesion excision	4532-0
Bowel excision/resection	3+5726
Colectomy	3+562-
Hernia repair	519855
Hydrocoele operation	46711-
Orchidopexy (bilateral)	467050
Orchidectomy (unilateral)	46+++3
Renal transplant	451873
Varicocele operation	467824
Vasectomy reversal	4677+6

III. MEDICATIONS WHICH MAY POTENTIALLY IMPAIR MALE FERTILITY

This is the list of the subset of medications reported at interview, with their associated Read codes, which may potentially impair male fertility:

Medication	Read code	Potential effects on male fertility
Adifax (fenfluramine)	15194-	Impotence and loss of libido
Aldomet (methyldopa)	0896-5	Failure of ejaculation
Amitriptyaline	14417-	Interference with sexual function
Anafanil	144240	Interference with sexual function
Asacol (mesalazine)	048144	Impotence
Atenolol	087547	Impotence
Ativan (lorazepam)	139---	Decreased libido
Axid (cimetidine type drug)	043-6-	Impotence
β blockers generic	087450	Impotence
Bendrofluazide	076566	Impotence
Benzalip	0-70-7	Impotence
Buserelin	287257	Decreased libido
Chlorpromazine (largactil)	1409-4	Impotence
Cimetidine	043806	Impotence
Clonidine	159467	Impotence
Clopixol	142189	Impotence
Cyclophosphamide	274214	Sterility*
Cyproterone	218344	Reversible decrease in spermatogenesis
Depixol	141026	Impotence
Diazepam	139810	Decreased libido
Flupenthixol	147455	Impotence
Gamamil	144433	Interference with sexual function
Haloperidol	141097	Impotence
Imipramine	144372	Interference with sexual function
Isocarboxazid	145332	Impaired sexual function
MAOIs generic	145236	Sexual dysfunction
Melleril (thioridizine)	141386	Impotence
Mianserin	1444-4	Interference with sexual function
Motival	146367	Sexual dysfunction
Nardil (phenelezine)	145271	Sexual dysfunction
Nitrazepam	138947	Decreased libido
Oxazepam	13-0-6	Decreased libido
Pindolol	087775	Impotence
Propanolol	087486	Impotence
Prothiaden	144301	Interference with sexual function
Prozac	147516	Sexual dysfunction
Raniditine	043841	Impotence
Salazopyrin	048240	Reversible azoospermia
Stelazine	141411	Impotence
Stemetil	154419	Impotence
Temazepam	138-08	Decreased libido
Testosterone	218440	Reversible decrease in spematogenesis
Tricyclic antidepressants	144144	Decreased libido
Trimipramine	144626	Interference with sexual function