Committee on Medical Aspects of Radiation in the Environment (COMARE)

EIGHTH REPORT

Review of pregnancy outcomes following preconceptional exposure to radiation.

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Produced by the National Radiological Protection Board
ISBN 0 85951 530 3

CONTENTS

FOREWORD

i The Committee on Medical Aspects of Radiation in the Environment (COMARE) was established in November 1985 in response to the final recommendation of the report of the Independent Advisory Group chaired by Sir Douglas Black (Black, 1984). Our terms of reference are to 'assess and advise Government and the Devolved Administrations on the health effects of natural and man-made radiation in the environment and to assess the adequacy of the available data and the need for further research'.

ii This, our Eighth Report, details our review of the scientific evidence and our advice on the possibility of adverse reproductive outcomes for radiation workers and their partners in the United Kingdom.

iii It was in our Second Report that we first recommended that epidemiological studies should be set up to consider any possible effects on the health of the offspring of parents occupationally exposed to radiation. In our Third Report we reiterated this recommendation and further stated that consideration should be given to broadening the scope of such studies to include the children in the largest sample of radiation workers. We noted the difficulty of carrying out such studies at that time given the paucity of available databases and recommended that an appropriate dialogue take place with the nuclear workforce to allow these studies to proceed whilst maintaining the necessary privacy of individuals.

iv In our Seventh Report we examined the results of all of the studies commissioned by the Co-ordinating Committee on Health Aspects of Radiation Research (CCHARR) which were concerned with the incidence of cancer in the offspring of irradiated parents. However, some of the studies commissioned by CCHARR also included an investigation of the adverse reproductive outcome of irradiated parents and we have been asked by the Department of Health and the Health and Safety Executive also to advise on this aspect of potential harm from radiation. We have considered the studies mentioned above and also other published data.

v In the preparation of this report the Committee requested data and information from a number of organisations and researchers. Many individuals have given time to present data to us and we wish to take this opportunity to thank all of them for their co-operation.

vi The views expressed in this report are those of the Committee and not necessarily those of the Secretariat, the Assessors, or those providing evidence. Technical detail is unavoidable in a report such as this, thus a glossary of terms is provided in Appendix A. A list of Committee Members, Transgenerational Effects Subcommittee Members, the Secretariat and Assessors is provided in Appendix B. A complete picture of the scientific background to this report, however, can only be gained by reference to the scientific material consulted. This is listed at the end of the report in the references.

EXECUTIVE SUMMARY

Introduction

1 Previous COMARE reports have looked at the effects of exposure to radiation in the environment on the risk of developing cancer in adults and children. This report examines the evidence for effects on pregnancy outcomes (called reproductive outcomes in the report) in the offspring of people exposed to radiation.

2 Animal and laboratory studies suggest that radiation exposure can increase the rate of certain conditions including malformations and death in the offspring of those exposed. However, studies of people exposed to radiation – for example, the Japanese atomic-bomb survivors – had not found clear evidence for such an effect. This could be because the animal studies generally use much higher doses of radiation and/or because the human studies were not powerful or well controlled enough to find an effect. This report re-examines the evidence including new research to try to determine if radiation exposure of parents can cause adverse pregnancy outcomes in their offspring.

What are adverse pregnancy outcomes?

3 The adverse pregnancy outcomes examined in this report include miscarriage, stillbirth, death in early infancy, congenital abnormalities, and alteration of the ratio of baby boys to girls. Overall, the incidence of stillbirth and early infant death has declined greatly in recent decades. It is already known that socioeconomic factors such as coming from a low income family, having very young parents, parents who smoke, or being first babies or one of multiple births are associated with a higher risk of adverse pregnancy outcome.

Effects of radiation on reproductive (germ) cells

4 Germ cells are the eggs and sperm produced by the ovary and testis. Experiments have shown that radiation can damage chromosomes in the germ cells. This damage includes loss of whole chromosomes or gross rearrangements of the chromosomes. Such changes are known to affect the fertility of the cells and the health of offspring. However, recently more subtle changes have been detected which can also be caused by radiation. These include loss of small fragments of chromosomes, loss and gain of repeated DNA sequences, and changes in gene expression (the extent to which the gene is transcribed and translated). The significance of these changes for human health is not yet understood but may suggest that radiation could cause more subtle damage than the range of adverse pregnancy outcomes listed above. Further research will throw light on whether the more subtle changes in chromosomes and gene expression induced by radiation are clinically significant in animals and humans.

Animal experiments on the effects of radiation on pregnancy outcome

5 It is difficult to study miscarriage and early infant death in laboratory animals but experiments on the effects of radiation on the incidence of severe congenital abnormalities have been done with mice. Radiation doses of around 1–5 Gy can double the background frequency of congenital abnormalities in mice but the frequency depends on the type of radiation, radiation dose, strain of mouse, and whether the male or female parent is irradiated. The types of congenital abnormalities induced include neural tube defects (spina bifida and

anencephaly). The radiation doses used in animal experiments are usually much higher than the environmental and occupational radiation doses to which humans are exposed.

Epidemiological studies of parents exposed to radiation

6 The studies of pregnancy in human parents exposed to radiation have not all looked at the same outcomes. Neither do they all use the same definition of important terms, such as the distinction between a miscarriage and a stillbirth. Therefore, a careful analysis is needed and it is often possible to reach only broad conclusions. The main groups of people studied are the atomic-bomb survivors, radiation workers, women who have previously had radiotherapy treatment, people living near uranium mines, medical radiologists and radiographers, and people living near nuclear reactors. Most of the studies of workers have looked at the effects of radiation exposure of fathers because fewer mothers have worked with radiation.

7 The studies do not draw identical conclusions but taken together they provide little evidence that adverse pregnancy outcomes in general are related to parental exposure to radiation at the relatively low doses to which most of the study populations have been exposed. Few of the studies have enough statistical power to address these issues (ie the doses are too low or the study populations are too small). The data do not indicate a link between congenital abnormalities as a whole and parental exposure to radiation. If there is an association, it is most likely a weak link between radiation exposure in fathers and increased stillbirths and neural tube defects (spina bifida and anencephaly) in their offspring. Increased risks for stillbirths and neural tube defects would be supported by data from animal experiments but have only been found in two independent human studies, both of nuclear workers (one at Sellafield in Cumbria and one in Hanford in the USA). They are not corroborated by similar findings from other studies or other nuclear sites. The radiation doses received by workers in the Sellafield and Hanford studies were higher than would be experienced by workers today. There is not enough evidence to say if these associations are also found in the offspring of irradiated mothers.

8 The other pregnancy outcomes studied (miscarriage or spontaneous abortion, neonatal death, congenital abnormalities as a whole, and the ratio of baby boys to girls) do not appear to be significantly associated with parental radiation exposure before conception. Many of the studies are difficult to interpret because apparent effects of radiation could really be due to other lifestyle and environmental factors that are known to affect the incidence of adverse pregnancy outcome. In principle, it remains possible that there could be a stronger effect that only occurs with radiation exposures at a certain time before conception or with a particular sort of radiation. Most of the studies were not powerful enough to detect any such effects.

Does parental exposure to radiation increase the risk of adverse pregnancy outcome at the doses to which the public and workers are exposed today?

9 Radiation workers in the UK are exposed to radiation doses of up to about 20 mSv each year. The maximum exposure corresponds to about ten times the average annual background radiation to which everyone in the UK is exposed each year. Most radiation workers have much lower exposures. The report uses all the research evidence to summarise the potential risks to the offspring of parents exposed to radiation doses typically received by radiation workers in the UK.

10 Animal experiments suggest that parental irradiation may increase the frequency of adverse pregnancy outcomes. However, the animal experiments are not necessarily a perfect model of how humans react to radiation, in part because the radiation doses used in these experiments are generally higher than doses to which humans are exposed.

11 Epidemiological studies in human parents provide little evidence that adverse pregnancy outcomes in general are related to parental exposure to radiation. If there is an association, it is most likely a link between paternal (not maternal) radiation exposure and incidence of stillbirths and neural tube defects (spina bifida and anencephaly). However, not all the relevant epidemiological studies reported such effects and the only human studies that did show these effects were conducted on two groups of workers who received higher radiation doses than workers experience today.

CHAPTER 1

INTRODUCTION

1.1 In 1984 the Black Advisory Group recommended a series of studies on individuals who had lived near the Sellafield nuclear site (Black, 1984). These included a recommendation for a case–control study to investigate relevant features of the records of cases of leukaemia and lymphoma in the area. This study was carried out by the MRC Epidemiology Unit in Southampton and published in 1990 (Gardner et al, 1990). The authors concluded that the raised incidence of leukaemia and non-Hodgkin's lymphoma (NHL) among children living in Seascale near Sellafield showed a statistically significant association with paternal employment at Sellafield and the recorded external radiation dose received prior to conception.

1.2 In our Seventh Report (COMARE, 2002) we examined the results of all of the studies commissioned by the Co-ordinating Committee on Health Aspects of Radiation Research (CCHARR). All of the CCHARR studies were commissioned to investigate the association suggested by Professor Gardner and his colleagues between the exposure of fathers to ionising radiation and the incidence of leukaemia or NHL in their children. However, some of the studies commissioned by CCHARR also included an investigation of the adverse birth outcome of children of irradiated parents and we have been asked by the Department of Health and the Health and Safety Executive also to advise on this aspect of potential harm from radiation.

Adverse reproductive outcome

1.3 *In vitro* and *in vivo* studies have demonstrated that ionising radiation can cause heritable damage which is expressed other than as an increased risk of developing cancer in the offspring. The types of damage expressed vary in different species but some types of damage are fairly consistent in animal models, such as changes in fetal death rates, infertility levels, miscarriage, sex ratios, and congenital abnormalities. In the major large epidemiological studies of humans exposed to ionising radiation, such as the studies of the Japanese atomic-bomb survivors, no clear evidence of this form of heritable damage has so far been demonstrated.

1.4 Pregnancy outcomes are affected by many factors (see Box 1). and epidemiological studies, are difficult to carry out for a variety of reasons. For example, a woman may undergo spontaneous abortion in the early weeks of pregnancy that will not be diagnosed as a miscarriage, either by the women herself or by her medical attendant. Thus reporting absolute levels of miscarriage is impossible. Nearly all such studies rely upon parents reporting the levels of adverse birth outcomes perhaps many years after the event and could be subject to various forms of bias. For example, men are less likely to accurately report such events as miscarriage in their wives or partners, than the women themselves, and it is thought that men are less likely to report infertility problems accurately. Such incomplete reporting is an inescapable part of epidemiological studies, although careful design and execution can minimise it. In recent years some such studies have been carried out in the UK and the USA using information gained from radiation workers. One of the epidemiological

studies funded by CCHARR was specifically designed to study the levels of stillbirth, miscarriage, congenital abnormality, infertility, and changes in sex ratio in a large section of the British radiation workforce. We have considered all of these recent studies in this report.

1.5 In summary, now that all the CCHARR studies are complete we have been asked by the Department of Health and the Health and Safety Executive to review all the evidence available for the existence of reproductive effects of ionising radiation at environmental levels in man. We have reviewed in depth the available genetic, biological and epidemiological evidence concerning adverse reproductive outcomes. Descriptions of this new work are contained in Chapters 2, 3 and 4, of this our Eighth Report. Our deliberations and conclusions concerning this topic are the subject of Chapters 5 and 6; our recommendations are contained in Chapter 7.

Box 1 What affects pregnancy outcome?

This report considers whether parental preconceptional irradiation (PPI) influences pregnancy outcome (miscarriage, stillbirth, congenital malformation, and neonatal death) and offspring gender ratio (number of boys : number of girls).

These investigations are complicated by the fact that many other factors can influence the risk of these outcomes and failure to fully consider these factors in any statistical analyses can lead to an underestimation or overestimation of the effect of parental preconceptional irradiation.

This box describes what we know about these factors and how they influence the outcomes under consideration (MacFarlane and Mugford, 2000).

Smoking

The babies of mothers who smoke during pregnancy are at higher risk of congenital malformation and death both during and after pregnancy than those of mothers who do not smoke. The rate of these adverse outcomes is generally reported to be increased by about 30% because of maternal smoking. Father's smoking may also put the baby at risk (especially during infancy) but the effect is not as great. Unfortunately, reliable information on parental smoking is very hard to obtain and most studies – especially those carried out retrospectively – have been unable to take parental smoking into account. However, there are well-known differences in smoking rates between people of different socioeconomic classes (those of higher socioeconomic classes tend to smoke less), and so consideration of socioeconomic class (see below) does address at least some of the smoking effect.

Socioeconomic status

Socioeconomic status is generally measured by the occupational social class of the head of the household (usually the father). There are large gradients in many health outcomes in relation to socioeconomic status and this is certainly true for pregnancy outcome. The rate of stillbirth and neonatal death is higher in mothers in the lower socioeconomic groups, although the magnitude of the social class effect varies between populations and with time. In the UK the rate of stillbirth was almost twice as high in mothers in the lower socioeconomic classes in the 1950s and 1960s, but now the difference is less marked – with around a 50% increased risk in the group at highest risk. In some countries – in particular, the Scandinavian countries – the effect of social class is much less than is seen in the UK.

Time trends

The risk of adverse pregnancy outcome has reduced dramatically over recent decades. In the 1950s in the UK some 50 babies out of every 1000 died either at birth or before the age of 1 year. In the year 2000 this fell to around 8 per 1000. The effect is more marked for deaths due to some specific causes than others: for example, there are fewer deaths due to complications during labour as management has improved, and fewer deaths due to congenital malformation as a result of elective termination following antenatal screening.

Parental age

The babies of both young mothers (under 20 years) and older mothers (over 35 years) are at increased risk. Miscarriage, stillbirth and neonatal death rates are all around 50% higher in older women and the risk of some congenital anomalies – in particular, Down's syndrome – increases dramatically with the age of the mother. In younger women adverse outcome is increased and, in particular, the risk of preterm birth is high and this is associated with an increased rate of neonatal death. Again, the age of the father may also influence pregnancy outcome, although the effect is less marked and more difficult to estimate since, in general, older fathers tend to be partnered with older mothers.

Gender ratio tends to fall with increasing paternal age – so older fathers are more likely to father girls than boys. This may be due to frequency of intercourse and consequently the timing of fertilisation within the cycle.

Birth order

The safest pregnancies are generally the second and third. First pregnancies are at the higher risk of adverse outcome (generally around 30% increased risk) as are the fourth and subsequent ones.

Birth order also influences the gender ratio: first babies are slightly more likely to be boys and later babies more likely to be girls.

Multiple pregnancies

Singleton pregnancies are much safer for the baby than twin or higher multiple pregnancies. The risk of adverse outcome is around ten times higher in twin pregnancies than singleton and the risk for triplets is even higher. Twin pregnancies occur naturally in about 1 in 80 pregnancies but in most countries the rate is increasing as a result of assisted conception.

CHAPTER 2

RADIATION-INDUCED CHANGES WITH POTENTIAL TO AFFECT REPRODUCTIVE OUTCOME

2.1 Fetal growth and development are susceptible to disruption by many factors, most notably by the nutrition and lifestyle of the mother. In this report, however, we are concerned primarily with effects on pregnancy outcome that have their origin before conception.

2.2 It has been general practice to consider exclusively mutational changes induced by radiation that take place during the production of the germ cells (egg and sperm). These changes, comprising gene mutations, changes in chromosome number, and deletion or rearrangement of chromosomal material, have been discussed in our Seventh Report (COMARE, 2002) and in various international consensus documents (eg UNSCEAR, 1993, 2000, 2001). A recent paper summarises the work of the major contributors to the theoretical development of genetic risk of ionising radiation (Sankaranarayanan and Chakraborty, 2000). These include some recent developments that may have implications for pregnancy outcome, some of which are outside the classical mutational paradigm and we shall touch briefly upon them in this chapter.

2.3 One area concerns 'chromosomal microdeletions', which are losses of small pieces of chromosome that may include several genes (including those sometimes called multilocus deletions) that have been difficult to characterise. In cellular and animal studies, radiation has been found to be relatively efficient at inducing such events in the germ line. However, only selected sites in the genome have been looked at and it is not clear whether microdeletions can be tolerated throughout the genome. In extrapolating these data to humans, where some microdeletion phenotypes have been described, it is difficult to know whether the radiation data can be applied to gene functions that are expected to affect the developing embryo. Sankaranarayanan (2001) has remarked that, despite their occurrence in different chromosomes, microdeletion phenotypes share some common features, eg mental retardation, growth retardation, specific patterns of dysmorphic features, and serious malformations. This led him to argue that the main adverse genetic effects of radiation are likely to be manifest in the progeny as multisystem developmental abnormalities which we call congenital abnormalities. Sankaranarayanan and Chakraborty (2000) drew on data from mouse studies on dominant skeletal defects, dominant cataracts, growth retardation and congenital malformations (Ehling, 1965; Selby and Selby, 1977; Kirk and Lyon, 1984; Searle and Beechey, 1986; Lyon and Renshaw, 1988; Nomura, 1988; Favor, 1989; Cattanach et al, 1993, 1995). Sankaranarayanan and Chakraborty (2000) made a provisional estimate of the risk of adverse developmental effects of about 2×10^{-3} per Gy for chronic low LET irradiation of either sex.

2.4 A second area, discussed in our Seventh Report, involves a type of genetic change that has only recently come to light in the context of radiation effects, namely the induction of changes at repeat sequences in DNA (eg minisatellites, microsatellites and tandem repeats). Most repeat sequences

are not in the coding parts of genes but some repeat sequences show radiation-induced changes in germ line cells that seem to be outside the classical paradigms in several respects. Firstly, the changes may occur at regions remote from that which sustains direct radiation damage. Secondly, the changes may occur in the progeny of the irradiated cell (ie the effect may be delayed). Thirdly, some of these DNA sequences show considerably greater sensitivity to radiation than do classical mutations. This hypersensitivity is, however, set against a background of spontaneous instability, the consequence of which is that the doubling dose (the dose at which the mutation frequency is increased to twice the naturally occurring frequency) is very similar to that for classical mutations.

2.5 These changes at repeat sequences and the problems involved in trying to assess their implications for health have been recently reviewed (Bridges, 2001; UNSCEAR, 2001). Clearly there is potential for such changes to affect the expression of adjacent genes even when the changes are not in the coding sequences. Maternal microsatellite alleles have been reported to affect the risk of spontaneous abortion (miscarriage) (Tsai et al, 1998) and several studies have shown that that microsatellite instability in the embryo is associated with spontaneous abortion (Kiaris et al, 1995; Spandidos et al, 1998; Nikitina and Nazarenko, 2000). The latter studies suggest the mutation rate at some microsatellite loci may be elevated both in the embryo itself and in the paternal germ line. Whatever the cause of the instability in these spontaneous abortions, this latter feature is consistent with radiation-induced repeat sequence instability in the mouse which can occur both in the germ line and in early embryonic cell divisions following germ line irradiation (Carls and Schiestl, 1999; Dubrova et al, 2000a,b; Niwa and Kominami, 2001; Berber et al, 2002; Shiraishi et al, 2002). Nevertheless, the literature on genetic instability and viability or morbidity of the developing embryo and fetus is still slender and few conclusions can be drawn at the present time.

2.6 The conventional approach to transgenerational effects has been to consider mutations in DNA sequence as discussed in the preceding paragraphs, but recent developments in technology (eg micro-arrays) have focused attention on epigenetics, the changes in gene expression which are not the result of changes in DNA sequence. These epigenetic changes may be transmitted through somatic cell divisions but are generally eliminated during germ cell development (cf. Holliday, 2001). If they are triggered prior to fertilisation, they could persist and influence embryonic development. Nomura (2001), using micro-array analysis, has recently reported that many functional genes were either suppressed or over-expressed in the offspring of mice exposed to radiation and Baulch et al (2001) have found changes in the levels of signalling protein kinases associated with reduced cell proliferation rates in the descendants of irradiated mice. There are several mechanisms involved in epigenetic effects. Some involve DNA, eg changes in methylation pattern; others involve modification of histones, eg acetylation, deacetylation or phosphorylation. Morgan et al (1999) and Rakyan et al (2003) reported transgenerational inheritance of epigenetic states in two different genes in the mouse, in both cases attributed to differential DNA methylation. In one of these genes, both maternal and paternal transmission was found, allowing a molecular model to be put forward for the inheritance of variable phenotypes according to DNA methylation status of sperm (Rakyan et al, 2003).

2.7 While radiation-induced epigenetic changes could in principle have profound effects upon the developing embryo and fetus, it is perhaps more likely that the effects may be more subtle. There might also be interaction between radiation-induced changes in gene expression and the various

environmental and lifestyle factors that influence pregnancy outcomes. This at least raises the possibility that there might be more subtle radiation-induced effects than those recorded in conventional studies (ie stillbirth, spontaneous abortion, major congenital abnormalities, etc). (See Box 1 in Chapter 1.)

Summary

2.8 In addition to classical radiation damage there is increasing evidence that other effects, some of them more subtle, may also be important. These include

(i) microdeletions as a source of congenital abnormalities,

(ii) the hypersensitivity of certain repeat sequences (the health consequences of which are unclear),

(iii) changes in gene expression (epigenetic effects) that affect embryonic development.

CHAPTER 3

LABORATORY STUDIES OF ADVERSE REPRODUCTIVE OUTCOMES FOLLOWING PARENTAL PRECONCEPTIONAL IRRADIATION

3.1 A number of adverse reproductive outcomes following parental irradiation have been studied in animal models. In this chapter we are considering four main categories of pregnancy outcome, namely miscarriage, stillbirth, offspring sex ratio, and congenital abnormality. This does not mean that more subtle effects (eg low birth weight) cannot occur. However, they are generally less easy to study, at least in animal models. It has been reported that parental (or gonadal) irradiation can increase the rate of intrauterine death in the offspring and also bring about a change in the ratio of male to female offspring in the next generation to that produced by unirradiated control animals (Luning et al, 1976). In a broad sense, late fetal death (stillbirth) may be regarded as a form of congenital abnormality and, as discussed elsewhere in this report, a proportion of human stillbirths carry malformations. Animal models have provided a considerable body of information relating to the induction of congenital abnormalities following parental irradiation, which is summarised below.

Induction of congenital abnormalities

3.2 The utility of laboratory rodents for studies on the multiple causes of stillbirth is severely limited because the mothers tend to eat any dead offspring present in their litters (UNSCEAR, 1993). The same behaviour applies to grossly abnormal offspring and, for this reason, mouse studies on the induction of congenital malformation by radiation and other agents frequently include fetal examinations shortly before birth.

3.3 Early studies on the induction by radiation of congenital malformation in mice have been considered by a variety of bodies and authors (Selby, 1990; UNSCEAR, 1993). Usually the emphasis has been placed on data inconsistency, high background rates in some strains and the segregation or variable expression of pre-existing mutations; problems of experimental design have also been identified. Overall, these early studies are not regarded as providing a sound basis on which to develop views on radiation risks. More recent and informative studies are considered here.

3.4 Nomura (1982, 1988) and Kirk and Lyon (1982, 1984) have published similar data on the incidence of congenital abnormalities following irradiation of different strains of mice. Irradiation of adult mice with doses of up to 5 Gy of acute X-rays was followed by mating with unirradiated mice at progressively longer intervals, to assess effects on different germ cell stages. The offspring of these matings were assessed by looking for abnormalities in late-stage fetuses in both studies, but Nomura also analysed 7-day-old offspring.

3.5 These studies showed that a significant induction of abnormalities occurred following irradiation, but that abnormality incidence varied with radiation dose, type of germ cell (male or female), germ cell stage, and time of assessment. For example, Nomura (1988) found that irradiation of mature male

germ cells (spermatozoa) gave a seven-fold induction of abnormalities at 2 Gy, while irradiation of progenitor male germ cells (spermatogonia) gave a four-fold induction at this dose. While the overall maximum incidence of abnormalities following irradiation of male germ cells was similar in the two studies, at around 2% abnormalities (Table 3.1), clear dose–response relationships were not always found due to high background levels of abnormalities (Kirk and Lyon, 1984). However, Nomura (1988) found that male germ cells showed an increasing incidence of abnormalities with doses up to 2 Gy followed by a lower incidence at 5 Gy (Table 3.1). Irradiated female germ cells showed an increased induction of abnormalities with dose over the whole dose range, with a maximum increase of about ten-fold when compared to unirradiated mice (Kirk and Lyon, 1982; Nomura, 1988). Overall the frequency of radiation-induced abnormalities was lower when assessed at seven days after birth than when assessed in fetuses, due to the death of some abnormal fetuses.

3.6 Many different abnormalities were identified in these mouse studies, with dwarfism and neural tube defects being common. Some of the non-lethal abnormalities were found to be heritable, including dwarfism, and it was suggested that this abnormality was caused by small chromosome deletions or rearrangements (Nomura, 1988; see also paragraph 2.3).

Table 3.1 X-ray induced congenital abnormalities following irradiation of mice (assessed in 19-day-old fetuses)

Strain/sex (stage)	Dose in Gy	Total number of live fetuses	Number abnormal (%)	Reference
ICR	0	1967	9 (0.5)	Nomura (1988)
ICR /male (spermatogonia)	0.36	163	1 (0.6)	
	1.08	234	3 (1.3)	
	2.16	496	9 (1.8)	
	5.04	170	2 (1.2)	
ICR /female (mature oocytes)	0.36	221	3 (1.4)	
	2.16	459	10 (2.2)	
	3.60	152	5 (3.3)	
	5.04	124	6 (4.8)	
3H1 /male (spermatogonia)*	0	720	5 (0.7)	Kirk and Lyon (1982, 1984)
	5	1014	22 (2.2)	
3H1 /female (mature oocytes)†	0	695	8 (1.2)	
	1.08	301	4 (1.4)	
	2.16	289	4 (1.4)	
	3.60	346	11 (3.2)	
	5.04	254	10 (3.9)	

* Experiment with high background control levels (see paragraph 3.5) not shown.

† Different unirradiated control sets were used for male and female studies by Kirk and Lyon.

3.7 Unweighted averages for the induction of congenital abnormalities by X-rays were about 4 x 10^{-3} per Gy for spermatogonia and about 9 x 10^{-3} per Gy for mature oocytes. Background levels of abnormalities were variable from experiment to experiment, but were comparable in the two mouse strains used. Taking background rates of around 0.5%–1% (5 x 10^{-3} – 10^{-2}) per generation, and assuming a linear dose–response, suggests a doubling dose for acute low LET radiation of around 1 Gy for the induction of abnormalities in both male and female mice. Dose fractionation studies of Nomura (1982) suggest that the induction of congenital abnormalities will be significantly reduced at low dose rates. Assuming a dose rate effectiveness factor of three (UNSCEAR, 1993) for genetic effects, these data, taken alone, would project a doubling dose of around 3 Gy for the genetic component of congenital abnormalities in mice. The intrinsic limits on the data, uncertainties on background rates and the variable penetrance or expressivity of the mutations, together with those associated with the comparability of mouse and human abnormalities, mean that this value should be used only to derive crude estimates of risk in humans.

3.8 Exposure of male mice of the Heiligenberger strain with 2.8 Gy gamma radiation before mating was reported to lead to a significant increase in malformed fetuses, namely gastroschises, a type of anomaly to which this strain is predisposed (Muller et al, 1999). This increase was observed primarily after exposure of meiotic germ cell stages and the authors argued that the limited germ cell stage data of Nomura and of Kirk and Lyon were also consistent with this result. Muller et al also reported an increase in preimplantation death and early resorptions following irradiation of spermatogonia at all stages except early spermatogonia. A similar result was obtained following irradiation of the zygote (Pils et al, 1999). Not only did these workers observe an increase in gastroschises in the mice exposed as zygotes, but when female mice exposed as zygotes were mated with unirradiated males, the rate of gastroschisis in the offspring was almost doubled (although it just failed to be statistically significant). There was also a significant increase is prenatal mortality, suggesting that the stimulus for anomalies might persist for more than one generation.

3.9 There are some parallels to this work in a series of studies with a mouse chimera system. In this system eight-cell embryos are irradiated and paired with non-irradiated control embryos to form chimeras which are cultivated for two to three cycles and then partially dissociated to obtain the number of progeny cells arising from the two partner embryos for each chimera. It has been found that cells from the embryo having an irradiated father have a small proliferative disadvantage in the developing embryo (Obasuju et al, 1988; Wiley et al, 1990) and that the target for this response is nuclear rather than cytoplasmic (Wiley et al, 1994a). Irradiation of type B spermatogonia (six weeks before mating) was most effective and a dose as low as 0.01 Gy yielded a significant decrease in proliferation (Obasuju et al, 1988).

3.10 It was argued that the effect observed was unexpectedly large for the dose given, if one were to assume a conventional mutational mechanism (Wiley et al, 1990). When similar experiments were carried out with densely ionising radiation, up to 47% of sperm (during post-irradiation weeks one and two) transmitted proliferation ratios that were at or below one standard deviation from the control means. Yet it was calculated that the proportion of sperm sustaining a hit from densely ionising ^{56}Fe nuclei was very much lower (5% for 0.1 Gy, 2.5% for 0.05 Gy, and 0.5% for 0.01 Gy) (Wiley et al, 1994b). The authors concluded that amplification from locally scattered radiation produced in the mouse and/or from diffusible chemical products arising from hit sperm and adjacent cells was involved. Quite how the proliferative

deficiency is mediated is unclear. There is evidence for changes in the expression of some protein kinases that might indicate an initial signal transduction process (Baulch et al, 2001) and there is evidence for involvement of the insulin-like growth factor I receptor (Peters et al, 1996). There is other evidence that the cells of offspring of irradiated male rodents differ from those of the offspring of unirradiated fathers. The cells of offspring of irradiated rats were shown to be more sensitive to the chromosome-breaking effect of radiation and cyclophosphamide (Vorobtsova, 2000), in line with other work in the Russian literature indicating deficiencies in the fitness of the offspring of irradiated rodents and *Drosophila* (cited by Vorobtsova, 2000).

3.11 The hypersensitivity of cells from irradiated fathers in the chimera assay is paralleled by hypersensitivity of the sperm of irradiated mice in fertilising oocytes. This has been reported with sperm produced six weeks after irradiation of the fathers (Burruel et al, 1997). The fertilisation defect was also seen in the sperm of the offspring of mice conceived with sperm from irradiated fathers. Similar transgenerational heritability has been reported with the chimera proliferation effect (Baulch et al, 2001, 2002), minisatellite instability (see Chapter 2), and congenital abnormalities in the Heilgenberger mouse strain (Pils et al, 1999). These recent results call to mind the old report of Luning et al (1976) which documented a similar hypersensitive induction of late intra-uterine deaths following treatment of the fathers with ^{239}Pu salts. Although all these effects appear to be heritable, in that they are manifest not only in the offspring of exposed fathers (the F1) but also in the offspring of the F1 mice (ie the F2), they clearly cannot be attributable to any sort of classical mutation.

Discussion

3.12 In spite of well-recognised uncertainties the data discussed above are valuable to this report in providing evidence that a dominantly expressing genetic contribution to congenital abnormality is inducible by radiation. It is notable that some of the congenital abnormalities (neural tube defects) induced in mice fall into the same general category as those reported in two epidemiological studies (Sever et al, 1988a; Parker et al, 1999) on the offspring of low dose, occupationally exposed radiation workers. These studies are discussed in the following chapter of this report.

3.13 In mouse studies conducted under carefully controlled laboratory conditions the presence of pre-existing susceptibility and/or environmental factors may be a cause of the variable background rates of congenital abnormality (UNSCEAR, 1988; Selby, 1990). These factors would be expected to be far more difficult to take into account in human epidemiological studies on possible effects of germ line irradiation.

3.14 Finally, although it is recognised that different inbred strains have different susceptibilities to genetic damage, the cytogenetic studies of Cattanach et al (1993, 1995) provide evidence of an association between growth-retardation and multilocus deletions (including microdeletions) from the germ line. Using these and human genetic data, Sankaranarayanan (1999) has argued that many such radiation-induced multilocus germ line losses will tend to compromise normal development, with growth retardation and developmental defects in offspring as the main features. It is expected, however, that a relatively high proportion of multilocus deletions will be lethal during embryogenesis and hence not recoverable as congenitally abnormal live offspring.

3.15 In summary, mouse genetic data support the view that ionising radiation can induce dominant mutations in the germ line, which express as congenital abnormalities in offspring. Quantification of these germ line effects

has not been straightforward largely because of variation in background rates but a genetic doubling dose of around 3 Gy for chronic low LET radiation may be estimated for male germ cells, albeit with substantial uncertainty. A multiple gene deletion mechanism may explain a significant fraction of congenital abnormalities induced in mice and the recoverability of such multilocus loss events (in humans and in mice) is expected to be limited by embryonic lethality. Overall, these studies also draw attention to the problems in establishing a baseline rate of congenital abnormality in studies on radiation effects in human populations.

Summary

3.16 Animal experiments have only looked only at severe effects on pregnancy outcome.

3.17 Such data as exist suggest that the doubling dose of chronic irradiation to induce congenital abnormalities is considered to be around 3 Gy (although the range is between 2 and 5 Gy).

3.18 There is little evidence on the shape of the dose–response above around 1 Gy, and no evidence below this level.

3.19 Other effects resulting from irradiation of rodent spermatogonia that might be relevant to pregnancy outcome in humans include a defect in cell proliferation in a chimera assay, a fertilisation defect, chromosomal hypersensitivity to radiation and cyclophosphamide, and instability at repeat DNA sequences. None of these effects is explicable in terms of conventional mutational events.

CHAPTER 4

EPIDEMIOLOGICAL STUDIES OF ADVERSE REPRODUCTIVE OUTCOMES FOLLOWING PARENTAL PRECONCEPTIONAL IRRADIATION

Background

4.1 In our Second and Third Reports (COMARE, 1988, 1989), we had recommended studies to investigate the health of workers in the nuclear industry. In the light of the report of Gardner et al (1990) the main focus of these studies became the incidence of childhood cancer, particularly leukaemia. Other effects concerned with pregnancy outcome were not, however, excluded from consideration and were an integral part of one of the studies set up in response to our recommendations. Several other studies have also addressed these adverse reproductive outcomes, many of which can also be referred to as untoward pregnancy outcomes. Adverse reproductive outcomes generally studied comprise fetal death (miscarriage and stillbirth), neonatal death (ie death within a short period after birth) and congenital abnormality (see Box 2). Changes to the ratio of the sexes of offspring as a possible consequence of parental exposure to radiation (see paragraphs 5.91–5.98) are also considered in this chapter. Some studies have considered perinatal death, ie they have combined stillbirth and neonatal death. Different researchers have used different terminology and, so far as possible, a standardised terminology is employed here. However, investigators have used different definitions of neonatal death, for example, death within the first seven or the first thirty days of life. Similarly, different researchers have used different criteria to distinguish stillbirth from miscarriage. In the UK the legal definition of stillbirth has, since October 1992, been death of a fetus at or after the twenty-fourth week of pregnancy; previously it had been the twenty-eighth week of pregnancy. The definition of 'congenital abnormality' also differs between studies. It should be noted that adverse reproductive outcomes generally have a variety of causes, including those with a substantial component of environmental and lifestyle influences.

Box 2 Definitions of adverse reproductive outcomes

Adverse reproductive outcomes are generally taken to include fetal death (miscarriage and stillbirth), neonatal death (ie death within a short period after birth, also called early natal death), congenital abnormality, and changes to the ratio of the sexes. This box gives more details of the definitions of these outcomes, as used in the UK. It is based on Macfarlane and Mugford (2000).

Fetal death can be divided into miscarriage and stillbirth. In the UK, the latter must be registered, as must live births. Stillbirth is defined as death of a fetus after the twenty-fourth week of pregnancy. Before 1 October 1992, fetal deaths before twenty-eight weeks of pregnancy were not registrable as stillbirths.

Neonatal death is defined as death within the first twenty-eight days of life. It is divided into early and late neonatal death. The former is death within the first seven days of life.

Perinatal deaths are stillbirths plus early neonatal deaths.

Infant death is death within the first year of life.

4.2 Studies of radiation as a possible factor in the aetiology of adverse reproductive outcomes have been carried out in a number of human populations. Individual studies often differ in their design and in the endpoints studied and comparisons can be complex. In addition, differences in the design of the studies inevitably mean that they are not all equally informative on the different endpoints. Some technical details from these studies are summarised in a separate table (COMARE, 2004), a simplified overview is given in the sections which follow. The more recent studies are discussed somewhat more fully. However, the original papers must be consulted if full details are required.

4.3 In describing these epidemiological studies, it is necessary to use some statistical concepts (for example, the probability or p-value). Explanations of such terms for non-specialist readers are given in the glossary.

The studies

Studies of survivors of the atomic bombings (Japan)

4.4 The survivors of the atomic bombings of Hiroshima and Nagasaki have been extensively studied to determine the somatic effects of exposure to radiation, but also to see whether genetic effects can be detected. A summary of papers relating to the latter work was published by Neel and Schull (1991). Two studies by the same group of workers will be considered here, that of Schull et al (1981) and that of Otake et al (1990). These considered cohorts of over 70,000 survivors. Two assessments of the radiation doses to survivors have been used, the TD65 assessments of 1965 (used by Schull et al) and the improved DS86 assessments of 1986 (used by Otake et al). It might be expected that the later analysis would supersede the earlier one. However, the former includes some more detailed analyses, not updated in the 1990 paper. The DS86 dose estimates are clearly superior to those of TD65 (Bartlett, 1982) but they are not the final best estimates and the doses are still being reviewed. Problems in the interpretation of data relating to survivors of the atomic bombings are discussed in Box 3 in Chapter 5.

4.5 The cohort consisted of a total of 70,082 pregnancies which lasted at least 20 weeks in the period 1948–1953. Infants were examined by a physician, generally in the home, and there was also an infant autopsy programme. About 30% of infants underwent a second examination at the Atomic Bomb Casualty Commission 8–10 months after birth. Of the total number of pregnancies, 34,117 were to parents neither of whom had been in the cities at the time of the bombings. In addition, a substantial number of pregnancies (23,791) involved parents neither of whose estimated dose exceeded 10 mSv. Thus only 12,174 pregnancies involved parents at least one of whom had been estimated to have received a dose exceeding 10 mSv. About 5200 fathers had preconceptional doses of 10 mSv or above.

4.6 The 1990 analysis considered the subset of 55,303 pregnancies for which DS86 dose estimates were available for both mothers and fathers. In only 10,069 of these did one or both of the parents exceed a dose of 10 mSv. Some of the analyses used conjoint gonadal dose, ie the sum of gonadal dose to the mother and to the father.

4.7 Otake et al (1990) considered adverse reproductive outcomes, defined as major congenital abnormality, stillbirth (later than 19 weeks) or neonatal death (called by the investigators ‘early natal death’, death within 14 days). There was a positive, non-significant trend for all adverse reproductive outcomes with conjoint parental DS86 dose. Little (1999) examined the trend of adverse reproductive outcomes by paternal dose; positive, but statistically non-significant, relative risks were again found, with and without allowance for maternal dose.

4.8 Otake et al also examined trends with conjoint parental gonadal dose for the various endpoints taken separately. They observed non-significant positive trends for stillbirth risk, neonatal death, and congenital malformation.

4.9 Schull et al (1981) studied adverse reproductive outcomes defined as major congenital abnormality, stillbirth or neonatal death (death within 30 days). They examined trends with dose using TD65 dosimetry and reported a non-significant inverse trend with maternal dose ($-9.6 \pm 6.5\ Sv^{-1}$). They also found a positive trend with paternal dose, large compared to the quoted standard error ($5.3 \pm 0.3\ Sv^{-1}$). However, the authors noted of these and some other findings that 'these regression coefficients have not been judged significant, despite their size relative to their standard errors because the observed frequencies of the events of interest are not significantly different initially'.

4.10 Schull et al found a statistically non-significant inverse trend of stillbirth risk with both paternal and maternal gonadal dose.

4.11 Schull et al also examined trends in risk of neonatal death and of congenital abnormality with paternal and maternal gonadal dose. For both endpoints they reported a positive trend with paternal gonadal dose and a inverse trend with maternal gonadal dose. None of these trends was statistically significant. It should be noted, however, that in this analysis neonatal deaths were defined as deaths within 30 days of birth, in contrast to the definition used by Otake et al (1990), of deaths within 15 days of birth.

Navajo mining cohort (USA)

4.12 Shields et al (1992) studied a Navajo population living in a uranium mining area around Shiprock in the Colorado Plateau. As well as occupational exposures in the mines, some of this population could have been exposed as a result of residence near mines or mine tailings. One hospital served most of the Navajo population living in the area and Shields et al reviewed hospital records for a series of over 13,000 births for the period 1964–1981. Information on congenital and perinatal conditions, stillbirths and infant deaths was abstracted. Shields et al compared rates for adverse reproductive outcomes with those in other native American populations and also conducted a nested case–control study.

4.13 Shields et al compared rates of congenital conditions with those available from other studies of Indian Health Service hospital records. However, for congenital conditions, the interpretation was complicated because the Shiprock series included information from the entire medical record, while ascertainment for the comparison groups was only up to the fifth day of life. The comparison groups were thus likely to have less complete ascertainment of congenital anomalies, particularly internal anomalies such as heart defects. A nested study of 266 cases of congenital abnormality and controls was also carried out. Cases were grouped into three categories according to *a priori* expectation of a link with radiation exposure; specific outcomes were also considered.

4.14 Shields et al presented data for all adverse reproductive outcomes taken together. Analyses were presented in terms of whether parents worked in a mine/mill, lived near tailings/dump, or lived near a mine. Relative risks for all three types of exposure were above unity. Only for mothers living near mine tailings/dump was the excess statistically significant (relative risk, RR = 1.83, 95% confidence interval, CI, 1.00–3.46). Much stronger associations were found with employment of mothers or fathers in a local electronics factory.

4.15 For almost all of the three outcome groups and potential risk factors the odds ratio was above one, but few of the elevations were significant. One

shortcoming of this study is that there is little information on radiation dose. For 14 of the 266 cases, the investigators were able to obtain information on occupational exposures to radon. These exposures were largely to the lung, but estimates of gonadal doses were also derived; these were in the range 12–68 mSv. Occupational dose information was available for 8 grandfathers as well as for the 14 fathers.

4.16 There was no association between those stillbirths which were not characterised by an identifiable anomaly and the father's preconceptional gonadal dose or work in uranium mines. However, these findings are based on a relatively small number of cases and so are of low statistical power.

4.17 There was no association of the risk of three groups of congenital malformations with the father's preconceptional gonadal dose or work in uranium mines. However, there were some indications of excess risk for mothers living near a uranium mine or mill. These findings are based on a fairly large number of cases (228 cases of congenital anomaly in live-born infants). However, there was little information on radiation dose in this study, so it is difficult to be sure of the power of the study in relation to assessing risks associated with paternal preconceptional exposure.

Haemangioma cohort (Sweden)

4.18 Källén et al (1998) studied the offspring of a group of about 18,000 Swedish women treated with radiotherapy for skin haemangioma in childhood. Estimates of radiation dose were available from treatment planning records. The women differed from the general population in having longer education and in smoking less. These are indications of higher social class, and this generally goes with lower risk of congenital abnormalities in children. An increased cancer risk, consistent with that estimated from the atomic-bomb survivors, has been reported in the women themselves.

4.19 The health of a total of about 19,500 of their children was determined by linking to the Swedish Registry of Congenital Malformations (it should be noted that the study was conducted while some of the women were still of child-bearing age). The mothers of 14,545 of these children had received ovarian doses of 10 mGy or more and 3,437 children had mothers whose doses had exceeded 100 mGy. Comparisons were made with national rates and also tests for trend with dose were carried out.

4.20 The endpoints considered by Källén et al were stillbirth, neonatal death, congenital malformation, and the sex ratio of offspring.

4.21 In comparison with national rates, there was a statistically significant excess of stillbirths (RR = 1.23, 95% CI 1.02–1.47) and a similar, but statistically non-significant, excess of neonatal deaths (RR = 1.20, 95% CI 0.98–1.46). However, there is no statistically significant trend in the risk of total perinatal mortality (stillbirth and neonatal death) with ovarian dose.

4.22 There was a slight excess of congenital malformations in the offspring of this group of women (960 observed versus 887 expected), but there was no trend of malformation risk with ovarian preconceptional dose. There was a statistically significant positive trend of neural tube defects with ovarian preconceptional dose in this study, but there was no overall excess prevalence at birth of this anomaly in the cohort (25 observed vs 22.8 expected). The authors examined more than 20 malformations or groups of malformations and suggested that the positive trend with dose for neural tube defects might be a result of multiple significance testing (see the glossary).

4.23 There was some evidence for an increased proportion of boys born to the most highly exposed group of women (ovarian dose above 500 mGy). However, the numbers were small (69 vs 53) and the result was not statistically significant.

Nuclear Industry Family Study (UK)

4.24 Those employees of the UK nuclear industry who have the potential for exposure to radiation ('radiation workers') wear film badges or other detectors and individual records of exposure to radiation are kept for them. This radiation dose is normally incurred over a long period of time so the exposures are generally more relevant to those of the public than are the short-term exposures of the atomic-bomb survivors, or those irradiated for medical purposes. In the Nuclear Industry Family Study (NIFS, see Roman et al, 1999), questionnaires were sent to a large number of workers from three organisations in the nuclear industry in order to identify, amongst other things, cases of cancer in their offspring. The organisations studied were the United Kingdom Atomic Energy Authority, British Nuclear Fuels plc and the Atomic Weapons Establishment. Workers employed at all three of these organisations during the study period (1993–1996) were included, as were those workers under 75 years of age with a pension entitlement at the first two. A total of 46,396 workers were approached and completed questionnaires were received from 36,050 (78%). Among workers assumed to have received a questionnaire the response rate was 82% for men and 88% for women.

4.25 A total of 23,446 workers (18,744 men and 4,702 women) reported that they had tried to have children and a large majority reported at least one pregnancy. Of these, 6,716 men and 520 women had been monitored before the estimated date of conception. The mean lifetime dose up to the estimated date of conception was about 10 mSv for men and 4 mSv for women. The NIFS considered about 10,000 pregnancies where the father's preconceptional dose was 10 mSv or more.

4.26 The NIFS investigated reproductive outcomes as well as childhood cancers (see our Seventh Report). Miscarriage and congenital malformations in offspring were examined according to parental monitoring at any time prior to conception. In particular, comparisons were made between conceptions before the parent was monitored for radiation exposure and those afterwards. Comparisons were also made between those who had accumulated different levels of preconceptional dose. Analyses were undertaken of early miscarriage (before 13 weeks), late miscarriage (13–24 weeks) and stillbirth (24 weeks and after). A validation study on a sample of adverse outcomes was conducted.

4.27 There was no evidence of increased risk of miscarriage in the partners of male radiation workers: rates were not raised in the pregnancies fathered by monitored workers compared to non-monitored workers, nor were rates higher in pregnancies fathered by the more highly exposed individuals. Female radiation workers reported higher levels of miscarriage in the first trimester (RR = 1.3, 95% CI 1.0–1.6). To investigate the results for mothers in more detail, analyses were carried out in terms of whether there was maternal employment or monitoring within six months of conception. The relative risk seemed to be higher in those pregnancies where the mother was monitored within six months of conception (and possibly during pregnancy). However, there was no trend with the level of total preconceptional dose. The relative risk of late miscarriage was below unity, but the difference was not significant.

4.28 As with miscarriage, there was no evidence for increased risk of stillbirth in the pregnancies fathered by men who were monitored before

conception, compared to the risk in pregnancies fathered by men who were not monitored before conception. A test for trend in stillbirth risk with the level of dose received by fathers before conception was positive but not statistically significant ($p = 0.09$). For pregnancies conceived by monitored mothers the risk of stillbirth was elevated and was on the borderline of statistical significance. The number of cases involved was too small to draw conclusions from the test for trend with dose.

4.29 The risks of stillbirth were below unity (but not significantly so) in mothers who were employed at the time of conception. For mothers who were monitored within six months of conception (and possibly during pregnancy) the relative risk of stillbirth was elevated but did not reach statistical significance.

4.30 The NIFS also examined rates of congenital abnormality in the children of employees of the nuclear industry before and after they were monitored for exposure to radiation (Doyle et al, 2000). There was no evidence of an increased risk of all major malformations taken together in offspring of men who were monitored, compared to those whose fathers were not monitored, before conception. Nor were risks significantly elevated for any of the diagnostic groupings (including neural tube defects for which the relative risk was close to unity). There were no significantly raised risks in the children of preconceptually-monitored mothers. However, the authors noted that numbers were small and that most relative risks were above unity.

4.31 Examination of the data by dose received by the mother or father before conception did not indicate any significant variation in risk.

4.32 The NIFS also investigated the sex ratio in children of nuclear workers (Maconochie et al, 2001). In contrast to the Cumbrian study, described below, no difference was found in the sex ratio of children of nuclear workers compared to children in the general population of England and Wales, or in the sex ratio of children born to parents who were monitored before their conception compared to children whose parents were not. Nor was there any trend with total preconceptional dose. However, there was no test for trend with dose in the three months before conception. The differences between the NIFS and the Cumbrian study are discussed in Chapter 5.

Cumbrian study (UK)

4.33 Parker and co-workers have established a database of all live births and stillbirths in Cumbria in the period 1950–1989 (later extended to 1991). Within this extended Cumbrian cohort, children of workers at the Sellafield nuclear reprocessing plant have been identified (Parker et al, 1997). This cohort was used to study stillbirths, including those with congenital abnormalities, and sex ratio. Within the study cohort there were about 3700 stillbirths amongst about 250,000 total births. Of these, 130 stillbirths and rather more than 9000 total births had fathers who had undertaken radiation work at the Sellafield nuclear plant. Cause of death was recorded on stillbirth registrations only from 1961.

4.34 Both a cohort and a nested case–control study were undertaken by Parker et al (1999). Information on occupational radiation exposure was available and was used in the analyses. For the cohort analyses, doses were available for whole calendar years; doses for shorter periods were estimated *pro rata*. For the case–control study detailed film badge records were used. The latter allowed a more accurate estimate of the dose in the 90 days before conception. The mean total preconceptional dose to the radiation workers was estimated to be about 30 mSv.

4.35 The stillbirth rate was non-significantly higher in the non-radiation-worker cohort than for radiation workers. This was accounted for by differences in social class and in the calendar period of births. There was a statistically significant association between stillbirth risk and father's radiation dose, both for the total preconceptional dose and for dose in the 90 days before conception. This was the case both for the whole calendar period (1950–1989) and for the period from 1961 onwards for which causes of death were available. For total preconceptional dose the p-value for elevation of the odds ratio in the adjusted analysis for the period 1950–1989 was 0.009; for 1961–1989 it was 0.018.

4.36 Stillbirth risk was investigated in the nested case–control study. Broadly similar results to the cohort study were found for the analysis in terms of total preconceptional dose (p-value for elevation of the odds ratio was 0.014). For analyses in terms of the dose in the 90 days before conception it was found that the more accurate 90-day doses (based on individual film badge results) lowered the mean dose to case fathers and increased those of controls so that the odds ratio was no longer elevated ($p = 0.37$).

4.37 Cohort analyses were performed of those stillbirths deemed to be due to congenital disorders (using the Alberman et al (1994) criteria) and for the subset of neural tube defects. Tests were carried out to look for trends with total parental preconceptional dose and the rate of congenital abnormalities. There was a trend with parental preconceptional dose for all congenital abnormalities at borderline levels of statistical significance ($p = 0.047$). The trend with neural tube defects was statistically significant. There was no analysis of congenital abnormalities in the case–control part of this study.

4.38 The Cumbrian cohort was used to compare the sex ratio of children born to the partners of men who worked at Sellafield as compared to other Cumbrian men (Dickinson et al, 1996). There were slightly more male children in the radiation worker group, and the increase seemed to be most marked in the children of those fathers receiving more than 10 mSv in the 90 days before conception. The authors were cautious in their interpretation, pointing out that the Sellafield fathers were somewhat younger than the rest, and that the estimates of 90-day preconceptional dose were approximate.

Study in Washington State (USA)

4.39 Sever and co-workers studied congenital malformations in Benton and Franklin counties in the south east of Washington State, near the Hanford nuclear plant. Congenital malformations were ascertained using a number of sources. For purposes of analysis these were combined into 12 groups. The investigators carried out both a case–control study of malformations in the offspring of Hanford employees (Sever et al, 1988a) and a general study of the prevalence at birth of congenital malformations in the area (Sever et al, 1988b). The prevalence study included 454 malformations occurring in 23,319 births in the period 1968–1980; comparisons were made with data from the Birth Defects Monitoring Programme in three states (Washington, Idaho and Oregon).

4.40 The case–control investigation (Sever et al, 1988a) included 672 cases diagnosed within the first year of life and 977 controls over the period 1957–1980. For cases 147 fathers and 48 mothers had been employed at Hanford before conception of the child; for controls the figures were 194 fathers and 58 mothers. A total of 52 fathers of cases and 73 fathers of controls had incurred a preconceptional dose of 10 mSv or more (rather more than a third of the total for both cases and controls). Only 2 mothers of cases and 1 mother of a control had a preconceptional dose of 10 mSv or above.

4.41 Observed and expected numbers of malformation cases were calculated for Hanford parents. For the categories of all malformations, all major malformations and neural tube defects the observed numbers were close to those expected. Two defects, dislocation of the hip and tracheoesophageal fistula, showed statistically significant associations with employment of parents at Hanford.

4.42 The test for trend between the rate of all malformations and parental radiation exposure was positive but not significant ($p = 0.07$); for all major malformations the association was not as strong ($p = 0.14$). For neural tube defects the association was statistically significant ($p = 0.04$). Neither dislocation of the hip nor tracheoesophageal fistula showed associations with parental radiation exposure.

4.43 For none of the 11 other health endpoints in the case–control study of Sever et al is there a statistically significant trend with parental preconceptional dose. In particular, there is no trend with parental preconceptional dose for the category 'all major malformations'. For these and other reasons Sever et al (1988a) were inclined to view the statistically significant trend of neural tube defects with parental preconceptional dose as most likely due to chance.

4.44 In the study of the prevalence of congenital abnormalities near the Hanford plant, Sever et al (1988b) observed a significant overall excess of neural tube defects, for births over the period 1968–1980 (rate 1.72 per 1000 births vs 0.99 per 1000 births in the comparison population). There was a significant deficit of cleft lip (0.59 vs 1.17 per 1000 births). Of the 40 cases of neural tube defects, only 7 had a mother or father working at Hanford before the infant was conceived. When the Hanford case–control study is analysed using the narrower time period considered in the prevalence study (1968–1980), there is no association between neural tube defects with parental preconceptional dose (Sever et al, 1988b). The investigators concluded that the observed excess over this period was unlikely to be explained by occupational exposure to ionising radiation (Sever et al, 1988b).

Radiographers Study (UK)

4.45 Roman et al (1996) studied pregnancy outcomes in a cohort of UK medical radiographers. Information was collected by postal questionnaire sent to 6730 members of the College of Radiographers. Completed questionnaires were received from just over 85%. Most responders (about 88%) were women. Information was provided on miscarriage (fetal death at less than 20 weeks), stillbirth and malformations in a total of about 9200 pregnancies. The number of congenital malformations reported was 163. It is important to note that no information on radiation exposure was available to the investigators. However, most medical radiographers receive very low doses (Hughes, 1999).

4.46 In the radiographers study, the proportion of miscarriages (12%) and of stillbirth (1%) were described as being broadly in line with findings from other studies. There was no statistically significantly elevated risk of major congenital abnormalities in the offspring of the radiographers. When comparisons were drawn with expected numbers calculated from data from the Liverpool Congenital Malformations Registry, the relative risks were unity for both the grouping of all major malformations and for Down's syndrome. Significantly elevated risks were reported for 'other musculoskeletal malformations' and 'chromosome abnormalities other than Down's syndrome'. The investigators noted that the findings were based on small numbers and should be interpreted with caution.

4.47 The number of cases born to fathers was small (23) and so the radiographers study had very little power to draw conclusions on any risks of paternal exposure.

Canadian congenital abnormalities study

4.48 Green et al (1997) carried out a case–control study of children with congenital abnormalities identified from the Canadian congenital abnormalities surveillance system. This is based on multiple sources of ascertainment. The parents of case and matched live-born control children were identified from birth records and linked with records of those employed by Ontario Hydro, a large company supplying electrical power. This yielded 341 links to fathers of cases and 426 links to fathers of controls (in 4 instances, both case and control fathers linked). For mothers, the numbers were much smaller (a total of 165 case plus control matches).

4.49 Records of occupational exposure to radiation were available. In 149 instances the case father had been monitored before conception of the child but the control father had not. In 177 instances the control father had been monitored but not the case father. This corresponds to a relative risk of 0.84 (CI 0.68–1.05). In 21 instances the case mother had been monitored before conception and/or during pregnancy while the control mother had not; in 12 instances the control mother had been monitored but not case mother. This corresponds to a relative risk of 1.75 (CI 0.85–3.55).

4.50 More detailed analyses were made of paternal preconceptional irradiation. Comparisons were made between those fathers with a preconceptional dose and those who were not monitored or had a zero preconceptional dose. Analyses were carried out in terms of total preconceptional dose (89 case fathers and 126 control fathers), dose in the six months before conception, and the dose from tritium in the sixty days before conception. Overall, and adjusted for father's age and history of stillbirths, there was a significant deficit of congenital abnormalities (RR = 0.72, CI 0.55–0.95) in offspring of fathers with a recorded preconceptional dose. Too few mothers of cases or of controls had recorded doses for analyses to be undertaken.

4.51 Analyses were carried out for a variety of aetiological groupings of congenital abnormalities (eg single gene disorders or chromosomal disorders) and also for groupings by ICD codings (eg abnormalities of the nervous system or of the facial region). Most relative risks were below unity and none of those above one approached a statistically significant elevation.

4.52 The mean total parental preconceptional dose to exposed case fathers was 39.9 mSv and the most exposed individual had received 262 mSv. For control fathers the corresponding figures were 38.7 and 307 mSv. However, analyses in terms of different (non-zero) dose categories were not presented.

Techa river populations (USSR)

4.53 Kossenko and Degteva (1994) carried out an analysis of pregnancy outcomes and early child mortality in a population living along the Techa river. These individuals were exposed to both internal and external radiation from the Soviet nuclear programme. The mean gonadal dose to a population of 20,000 or more was estimated to be 0.16 Sv. Kossenko and Degteva reported no decrease in fertility or birth rate, nor were there differences between the exposed population and controls in the incidence of spontaneous abortion (miscarriage) and stillbirths.

4.54 Reported congenital abnormality rates were low. However, the authors noted that congenital abnormalities were inadequately diagnosed in rural areas in the 1950s and 1960s. They therefore considered early natal mortality from all endogenous causes (labour complications, congenital abnormalities and perinatal mortality from unidentified causes). This was twice as high in a group with a mean parental gonadal dose of 0.11 Sv as in the control group. Rates in a group with a mean parental gonadal dose of 0.045 Sv were slightly higher than in controls.

4.55 However, later studies suggest that both the dosimetry and the follow-up of the cohort could be improved (Degteva et al, 2002; Kossenko et al, 2002). Revised analyses have not yet been published.

Studies of the children of survivors of cancer

4.56 Many people who develop cancer are now successfully treated and go on to have children. The treatment will frequently have involved high radiation doses to part of the body. Records of these radiation treatments are nearly always available, although the records are likely to be complex and their interpretation can be very difficult. If chemotherapy was also given, the interpretation is again more complicated. If radiation exposure of parents does result in adverse reproductive outcomes, the effects might be seen in the offspring of these patients. The study by Källén et al (1998), discussed above, is of this type. We note, however, that interpretation of studies of the children of cancer survivors is generally very difficult.

4.57 One of the largest of these is the 'Five Centre Study' by Byrne et al (1998). They reported on genetic disease in the offspring of over 1000 survivors of childhood cancer as compared to those of about 2000 controls. This cohort has been used for a study of cancer as well as genetic disease in the offspring of survivors. Genetic disease was taken to mean cytogenetic syndromes, single gene defects, or one of fifteen common simple birth defects.

4.58 There were about 2200 eligible offspring of the cancer patients and 4500 offspring of controls. The rate of genetic disease in the offspring of survivors was 3.4%; for controls the figure was 3.1% which is not significantly different. Similarly, there was no significant difference between levels of genetic disease in the offspring of male patients and controls or of female patients and controls. Nor were there significant difference for any of the three classes of genetic disease: cytogenetic syndromes, single gene defects, or simple birth defects.

4.59 There was no significant difference in the sex ratio of offspring born to male or to female patients as compared to controls.

Summary

4.60 Adverse reproductive outcomes comprise a variety of conditions of diverse aetiology. Lifestyle and environmental factors undoubtedly play an important part in some conditions and rates change with time. These factors complicate the interpretation of epidemiological studies. Most of the evidence relates to the consequences of irradiation of fathers rather than of mothers.

4.61 Studies of adverse reproductive outcomes in offspring of survivors of the atomic bombs have various methodological problems and have produced weak and inconclusive evidence.

4.62 The epidemiological studies have not been analysed in such a way as to allow the reliable estimation of a 'doubling dose' which is often estimated in laboratory studies.

4.63 A large study of UK nuclear workers in Cumbria reported an association between stillbirth and paternal preconceptional dose. The association appeared to be most marked in stillbirths due to neural tube defects in the child. The Cumbrian study also found some evidence for an increased proportion of boys in the offspring of irradiated fathers.

4.64 Studies around the Hanford plant in the USA found some evidence for increased rates of neural tube defects, but not of other abnormalities, in the offspring of fathers who received higher doses of radiation.

4.65 Another large study of UK nuclear workers (the Nuclear Industry Family Study), in contrast to the Cumbrian study, found no association between stillbirth and parental preconceptional irradiation.

4.66 A case–control study of congenital abnormalities in Canada found no evidence for an association with paternal preconceptional irradiation.

4.67 A Swedish study examined the offspring of women who had been irradiated in childhood. Evidence from this study was hard to interpret but included the possibility of an association between maternal irradiation and neural tube defects.

4.68 A number of other studies (of UK radiographers and of a Navajo mining population) were negative, but lacked the power to throw significant light on these questions. Studies of the offspring of survivors of cancer were also negative, but interpretation of the results requires care.

CHAPTER 5

DISCUSSION

5.1 This chapter presents a discussion of the evidence summarised in Chapter 3 on laboratory studies and in Chapter 4 on epidemiological studies concerning adverse reproductive outcomes in the offspring of irradiated parents. As described in Chapter 4, adverse reproductive outcomes are taken to comprise miscarriage, stillbirth, neonatal death (ie death within a short period after birth), and congenital abnormality. Changes in the ratio of the sexes of live-born offspring are also considered. We will start by considering the evidence from epidemiology.

5.2 As described in Chapter 4, epidemiology can throw light on fetal death (miscarriage and stillbirth) and on neonatal death. However, comparisons between different studies are complicated because different researchers have used different nomenclature and have also studied different endpoints. Thus different definitions of neonatal death are in use – for example, death within the first seven or the first thirty days of life. The definition of 'congenital abnormality' also differs between studies. Some types of congenital abnormality are so serious that the baby may not be born alive or may die shortly after birth and there is thus overlap with other types of adverse reproductive outcomes. Box 2 in Chapter 4 gives the standard definitions of types of adverse reproductive outcomes which are in use in the UK.

5.3 Most studies discussed here are of the possible effects of irradiation of men but some involve women. It is important to remember that the effects, if any, of preconceptional exposure to radiation on pregnancy outcomes may be quite different in the two sexes. It is also very possible that any effect will vary with the preconceptional period during which irradiation occurs. This is particularly the case for irradiation of men, since there are distinct stages in the development of mature sperm from the spermatogonia.

5.4 The statistical power of studies to give information on possible adverse reproductive outcomes is determined by the number of subjects and by the magnitude of the doses involved (see the glossary). As with all epidemiological studies, the possibility for bias and confounding must be considered and it is important to consider whether other sources of information provide support for any particular finding (Bradford Hill, 1965). The play of chance may result in apparently significant findings when there is no causal link between the agent being investigated and the endpoint. This danger is particularly acute when multiple significance tests are made (see the glossary). Conversely, random factors may mean that a well-conducted study fails to confirm a risk which is, in fact, a real one.

5.5 In the discussion which follows, we are primarily concerned with predicting effects that may occur at the levels of exposure which workers and members of the public normally receive. If a certain effect is not seen in workers exposed at a rate of a few mSv per year (even a few tens of mSv per year) it does not follow that it could not arise if, for example, doses of several hundred mSv were received acutely as a result of an accident.

Box 3 Interpretation of studies of the atomic-bomb survivors

There are well-known problems in the interpretation of studies of the effects of radiation on the survivors of the atomic bombings. Some relate to estimates of the effects on survivors and some relate to the way that this information is applied in other circumstances.

(i) There are uncertainties in the estimates of dose and in the role of neutrons.

(ii) Follow-up did not start until some time after the bombings.

(iii) The possibility of effects from blast or heat from the weapons and from malnutrition at the end of the war must be remembered.

(iv) The study is of a Japanese population and the spectrum of congenital abnormalities is not necessarily the same as in other populations. There are uncertainties about the way in which consequences for other populations should be extrapolated from data about post-war Japan.

(v) Almost all of the dose was incurred effectively instantaneously; there are uncertainties in drawing inferences for chronic low dose rate exposures.

Nevertheless, the cohort is large, it includes all ages and both sexes, and there was a wide spectrum of doses. It would be expected that studies of adverse reproductive outcomes in this cohort would be important just as they are for studies of the induction of cancer.

We note, however, that collection of data on adverse reproductive outcomes began in 1948. Studies of the atomic-bomb survivors can therefore give no information on effects which manifest themselves only in the first three years or so after exposure, including effects which would result from exposure of the more mature germ cell stages such as spermatocytes, spermatids and spermatozoa. Conversely, the delay means that there should be no confounding with the acute effects of blast or heat from the weapons or from the social conditions at the time of the bombings.

Two particular points relating to these studies of adverse reproductive outcomes in children of the atomic-bomb survivors should be noted. The studies include pregnancies terminating in the years from 1948 to 1953. A proportion of these, particularly in the later years, will have involved fathers who were pre-pubescent in 1945. It cannot be assumed that the effects of irradiation at these young ages is the same as for adult men.

Some of the acute doses may also have been large enough to induce permanent sterility. This would reduce the number of births in the high dose groups and reduce the power of the studies.

A particular problem relates to the estimates of doses incurred by atomic-bomb survivors. For many years, the best estimates were known as ‘TD65’ (Tentative Dose estimates of 1965). These were superseded by ‘DS86’ (the Dosimetry System of 1986). This will, in turn, be superseded by new dose estimates in the next few years.

The two main studies of adverse reproductive outcomes in the atomic-bomb survivors were those of Schull et al (1981) and Otake et al (1990). The former used TD65; the latter, DS86. The later analysis would, other things being equal, be preferred. However, while Schull et al presented separate analyses in terms of doses to fathers and of doses to mothers, Otake et al used conjoint dose (the sum of doses to both parents). We wish to consider separately the effects of irradiation of men and of women and the work of Otake et al is therefore less informative.

The question then arises of whether the differences between TD65 and DS86 doses are so large that analyses based on the former must now be ignored. Comparisons with the changes in risk estimates for cancers should help to throw light on this question. Preston and Pierce (1988) reported that the excess relative risk (ERR) for solid cancers per gray (intestinal dose) changed from 0.80 using TD65 doses to 0.60 using DS86. For leukaemia the ERR per gray (bone marrow dose) changed from 3.52 to 3.23. For these somatic effects, analyses in terms of TD65 were thus not greatly dissimilar to those in terms of DS86. It therefore appears not unreasonable to assume that the analyses of Schull et al (1981) on pregnancy outcomes are still informative on the question of possible associations between adverse reproductive outcomes and parental irradiation, although it would be wise to regard the uncertainties as rather wider than those reported.

Otake et al (1990) also compared analyses of the effects of different dosimetry systems on predictions of the effects of conjoint parental dose on untoward pregnancy outcomes. Using TD65 the regression coefficient was 0.0018 (± 0.0032); using DS86 it was 0.0026 (± 0.0028). Again, this suggests that the earlier dosimetry gives results which are similar to those based on DS86.

The two published analyses of adverse reproductive outcomes in the offspring of the atomic-bomb survivors use linear adjustment for covariates such as birth order. More modern analytical techniques would be preferred. We understand that a new analysis, based on a revision of dosimetry and updated in other respects, is in preparation. Nevertheless, with the caveats above, we continue to regard evidence from the atomic-bomb survivors as relevant to the topic of this report.

5.6 In animal studies it is possible to study effects associated with a very large range of exposures. It is also, in principle, possible to do many experiments and so to understand the exact nature of the relation between dose and effect – the dose–response curve. In human studies this is invariably not the case; the range of exposures studied is limited and the number of studies is small. Thus even when there are significant findings of a relationship between dose and outcome, there may remain uncertainty about the precise shape of the dose–response curve. The results of animal studies are sometimes presented in terms of the 'doubling dose', that dose at which the natural mutation frequency is doubled. This quantity can almost never be measured directly in human studies, although mathematical models can be used to estimate it.

5.7 In high dose studies, fetal death may complicate the interpretation of dose–response relationships. It is possible that high levels of exposure to a reproductive toxin may result in fetal death and distort relationships between potentially toxic exposures and reproductive outcome (see, for example, Selevan and Lemasters, 1987).

5.8 In most of the analyses we have referred to, and in our summary comments, we have considered broad groupings of congenital abnormalities. Sometimes we have considered all congenital abnormalities taken together as though they represented one possible type of adverse outcome. In view of the diverse nature and diverse aetiologies of these conditions it is extremely improbable that they will be similarly affected by parental preconceptional irradiation, and it can be reasonably argued that to group them together could provide at best an insensitive measure of radiation effects. Against this, we would argue that, from the viewpoint of public health and radiation protection, the question to be answered is whether the total risk of adverse outcomes is increased by parental preconceptional irradiation, and that this measure is therefore relevant to such concerns. The ideal of analysing each type of outcome separately is, in fact, frequently not an option. Firstly, in many of the studies we have considered the data are not presented in sufficient detail; secondly, the numbers of abnormalities of individual types would in most cases be too small for a separate analysis to have adequate statistical power.

5.9 Perhaps the most important sources of information on the somatic effects of radiation, particularly cancer, are studies of the survivors of the atomic bombings of Hiroshima and Nagasaki. The problems in the interpretation of studies of adverse reproductive outcomes in the atomic-bomb survivors are discussed in Box 3. Evidence on the possible induction of adverse reproductive outcomes by radiation also comes from studies of other groups, including those exposed at work or from medical or environmental sources. These studies will also have strengths and weaknesses.

Adverse reproductive outcomes in general

5.10 Few epidemiological studies have considered the grouping of all adverse reproductive outcomes (ie miscarriage, stillbirth, neonatal death, and congenital abnormalities) taken together.

5.11 Both Schull et al (1981) and Otake et al (1990) reported on adverse reproductive outcomes in the survivors of the atomic bombings of Hiroshima and Nagasaki. In the case of Schull et al (1981), early natal death in the first month after birth was considered; Otake et al (1990) took early natal death in the first 14 days only. Schull et al used the TD65 dose estimates, while Otake et al used the later DS86 estimates. Despite these differences, there is very substantial overlap between the two analyses. As noted above, the earlier paper includes some more detailed analyses which were not updated by Otake et al.

5.12 Schull et al (1981) reported a non-significant inverse trend for adverse reproductive outcomes with maternal dose ($-9.6 \pm 6.5\ Sv^{-1}$). An inverse (or 'negative') trend is one in which there are relatively fewer cases with increasing dose. They found a positive trend with paternal dose, large compared to the quoted standard error ($5.3 \pm 0.3\ Sv^{-1}$). However, the authors judged the observation non-significant (see paragraph 4.9). If this was on the basis that there was no overall excess of abnormalities in the offspring of exposed fathers as compared to the unexposed, this judgement could be challenged. It is possible to have a significant dose–response relationship without a significant absolute excess, especially where rare outcomes are being considered and where most of the exposures are in the lower part of the dose range.

5.13 Otake et al (1990) reported a positive, non-significant trend for all adverse reproductive outcomes with conjoint parental DS86 dose. Little (1999) examined the trend of adverse reproductive outcomes by paternal dose, with and without allowance for maternal dose, using different risk models; positive, non-significant relative risks were found in all cases.

5.14 The Japanese dataset thus provides no statistically significant evidence for a link between adverse reproductive outcomes and radiation exposure. There was a suggestion of an inverse association with maternal irradiation and a suggestion of a positive association with paternal irradiation.

5.15 Shields et al (1992) studied birth defects, stillbirths, infant deaths and other adverse reproductive outcomes in a Navajo population from a mining area. No results were reported which plausibly suggested an effect of radiation exposure.

5.16 There is no significant evidence from the few published studies that irradiation of either fathers or mothers results in adverse reproductive outcomes in general. If such deleterious effects do occur, we judge that they would be seen more clearly in studies of specific endpoints.

Miscarriage

5.17 Information on the early death of the fetus is less easily obtained than for some of the other endpoints discussed in this chapter. Of the studies considered here, only the Nuclear Industry Family Study (NIFS) and the radiographers study have examined miscarriage rates. The latter reported that miscarriage rates in radiographers were not unusual. There was no dosimetric information in the radiographers study, but it is likely that exposures were low.

5.18 In the NIFS (Doyle et al, 2000), comparisons were made between rates of miscarriage in workers after they were employed in radiation work in the nuclear industry with rates beforehand. There was no indication of abnormal rates in pregnancies of the partners of male radiation workers, in either the first or second trimester (1416 and 379 miscarriages, respectively, in the partners of monitored workers). Relative risks were all close to one, with confidence intervals which included unity.

5.19 Female radiation workers reported elevated miscarriage rates in the first trimester. There were 117 reported miscarriages among monitored women in this period, the relative risk being 1.3 (CI 1.0–1.6). In the second trimester, there were fewer miscarriages than expected, although the deficit was not significant. In the first trimester, the relative risk seemed to be higher in those monitored around the time of conception, but there was no apparent correlation with total preconceptional dose. We note that doses incurred by female radiation workers are usually lower than those to men and it is difficult to draw conclusions for more highly exposed populations.

5.20 These limited data provide no significant evidence that miscarriage is a result of parental irradiation.

Stillbirth

5.21 Stillbirth itself is a heterogeneous outcome. Some stillbirths are associated with congenital malformation, some with maternal conditions such as pre-eclampsia, and some are unexplained. Stillbirth rates also vary greatly from one area to another and have been reported to be associated with the age of the father, age of the mother, sex of the child, birth order, year of birth, and other, deprivation-related, factors. It is desirable to allow for such concomitant factors, but it is difficult to do so completely.

5.22 Several datasets contribute information on whether stillbirth is associated with parental exposure to radiation.

5.23 Two analyses of stillbirth in the offspring of the atomic-bomb survivors have been published. Overall, these studies certainly provide no convincing evidence for an association between parental exposure and stillbirth, but neither do they provide significant evidence against such a possibility.

5.24 In the study of a cohort of women who had received radiation treatment for skin haemangiomas before the age of 18 months, there was an elevated risk of stillbirth when comparisons were made with national rates, but it was not related to the level of exposure (Källén et al, 1998).

5.25 Doyle et al (2000) studied stillbirths in the Nuclear Industry Family Study (NIFS). The NIFS considered both radiation workers and others employed by parts of the UK nuclear industry. Radiation workers are those more likely to be exposed to radiation and who wear badges to assess their exposures and for whom radiation dose records are kept. As with miscarriage, there was little evidence for increased levels of stillbirth in the partners of male radiation workers. A total of 152 stillbirths were reported in the partners of monitored men, corresponding to a relative risk of 1.1 (CI 0.8–1.4). The investigators reported that there was little evidence for an increase in stillbirth risk with increasing dose. We note, however, that the trend was positive, although not significant ($p = 0.09$).

5.26 We note correspondence in the *Lancet* relating to the NIFS (Doyle et al, 2001a; Parker, 2001) in which it was suggested that the levels of stillbirth reported by NIFS participants were so low as to cast doubt on the findings of the study. This was not accepted by the NIFS authors who suggested that differences in the socioeconomic status of the populations studied invalidated simple comparisons between the NIFS and the Cumbrian study. We have noted that the possibility of chance, bias or confounding must be considered in the evaluation of any epidemiological study.

5.27 For pregnancies conceived by monitored mothers the risk of stillbirth was elevated and was on the borderline of statistical significance. The number of cases involved was too small to draw conclusions from the test for trend with dose. The risks of stillbirth were below unity (but not significantly so) in mothers who were employed at the time of conception. For mothers who were monitored within six months of conception (and possibly during pregnancy) the relative risk of stillbirth was elevated but did not reach statistical significance.

5.28 Parker et al (1999) examined stillbirths in Cumbria, with particular reference to fathers' exposures to radiation if employed at the Sellafield nuclear plant. Stillbirth rates were not elevated in radiation workers compared to

non-radiation workers employed at Sellafield. However, in a cohort analysis, an association was found between stillbirth and both total preconceptional dose and dose in the 90 days before conception. In an analysis in which adjustments were made for possible confounding factors the odds ratios* per 100 mSv were 1.24 (CI 1.04–1.45, p = 0.009) and 1.86 (CI 1.21–2.76, p = 0.003), respectively. However, in the case–control study, which used more accurate estimates of dose, only the association with total preconceptional dose was seen.

5.29 We note that the results of Parker et al provide stronger evidence for a link with total parental preconceptional dose than with dose in the 90 days before conception. If there were a causal relation between stillbirth and cumulative parental preconceptional dose, this would suggest that it is the dose to the spermatagonial stem cells which is of relevance. The implication is that it would be biologically valid to compare with the offspring of the atomic-bomb survivors since these children would result from a conception involving sperm originating from stem cells exposed during the explosions.

5.30 The relative risks for stillbirth per 100 mSv total preconceptional dose reported by Parker et al were 1.24 in the cohort analysis and 1.30 in the case–control analysis. These risks are larger than have been found in other studies, most of which have not reported significant associations. In particular, Abrahamson and Tawn (2001) suggest that the overall excess of stillbirths (17.5, 95% CI 3.1–31.9) reported by Parker et al is much larger than that expected from other radiation genetic risk models. However, Abrahamson and Tawn have not considered a possible role for unconventional genetic mechanisms of the kind that we have discussed above.

5.31 It has been suggested (Little, 1999) that the results of Parker et al are statistically incompatible with those of the atomic-bomb survivors whether a relative risk analysis or an absolute risk analysis (Pearce et al, 2002) is carried out. However, it is likely that a fuller allowance for factors such as the influence of concomitant variables might significantly widen the confidence intervals reported by most studies. For example, we have noted above that the use of the older TD65 doses in analyses of the atomic-bomb survivors means that the uncertainties in these results are also likely to have been underestimated. We have noted also above the difficulties in generalising results from the atomic-bomb survivors to a western working population.

5.32 There are three other significant aspects of the results of Parker et al that should be noted.

(i) The statistical association of stillbirth with father's dose was driven by the frequency among the offspring of those fathers who had received the highest exposures. Lower doses were ineffective and the apparent effect was not related to dose in a linear manner, ie there might have been a threshold for the effect. Whether or not this is the case, the predicted effect at lower doses depends on the dose–response model chosen.

(ii) During the period of the study the overall frequency of stillbirth decreased by a factor of around five. The authors made statistical

* When odds ratios based on a continuous linear relationship between the dose and the logarithm of the response are reported it is possible to work out the anticipated effect at any dose based on the statistical model. For an odds ratio of 1.24 per 100 mSv, as observed in this study, for example, the effect estimate at 500 mSv is $1.24^{500/100} = 2.93$. It would therefore be possible to work out the doubling dose (here around 350 mSv). But it might be incautious to do so since it implies more knowledge than we may have about the shape of the dose–response.

corrections for year of birth as well as social class, father's age and birth order. Nevertheless, there must be some concerns that the corrections made for this very marked temporal trend were incomplete and that some residual confounding remains.

(iii) Because the highest doses were received by fathers at a time when natural stillbirth rates were very high, presumably due to the operation of factors operating during pregnancy itself rather than on the father's germ cells, one may speculate that any preconceptional effect on the latter might only be detectable when stillbirth rates are high. This would represent an interaction between preconceptional irradiation and environmental or lifestyle (eg dietary) factors influencing pregnancy outcome.

5.33 Stillbirth was studied in the offspring of UK radiographers (Roman et al, 1996). This study did not have access to information on radiation exposures, but the doses involved were certainly much lower than those received by the atomic-bomb survivors or nuclear workers. No evidence for increased levels of stillbirth was reported, but the implications of this observation for more highly exposed populations are limited.

5.34 Similarly, the study by Shields et al (1992) of the offspring of a Navajo population living in a uranium mining area gave no support to the hypothesis of a link between parental preconceptional irradiation and stillbirth, although there is very little dosimetric information and estimates of the statistical power of the study are difficult.

5.35 Does irradiation of men result in increased levels of stillbirth in pregnancies of their partners? Neither studies of the atomic-bomb survivors nor the NIFS suggest that this is the case. However, the Cumbrian study of Parker et al reported a significant dose-related effect and appears to be in conflict with studies of the atomic-bomb survivors and the NIFS. We do not regard the other studies discussed above as providing strong evidence on this question. We note that stillbirth rates are affected by a number of non-genetic factors (eg maternal care, diet and smoking during pregnancy) and have been changing substantially with time. The Cumbrian study of Parker et al attempted to allow for such factors, but could not do so completely. This may mean that the statistically computed confidence intervals reported for this study are too narrow. However, controlling for covariates is never complete and studies of the atomic-bomb survivors may also have wider confidence intervals than those reported.

5.36 Thus, considerable uncertainties remain as to whether there is a relationship between paternal preconceptional irradiation and stillbirth.

5.37 There is less information relating to a possible link between maternal irradiation and stillbirth. There is again no evidence from the atomic-bomb survivors to support such a suggestion. Both the Swedish haemangioma study (Källén et al, 1998) and the NIFS provided some evidence for elevated levels of stillbirth but not for an effect which increased with radiation dose. We regard the evidence for such an association as weak.

Neonatal death

5.38 Studies of neonatal death are less common than those of stillbirth. In studies of the atomic-bomb survivors, Otake et al (1990) observed a statistically non-significant positive trend of the risk of neonatal death (death within the first 15 days) with the sum of gonadal doses to the father and the mother. The analysis by Schull et al (1981), based on earlier dosimetry, defined neonatal deaths as within 30 days of birth. It showed statistically non-significant trends which were positive with paternal gonadal dose and negative with maternal gonadal dose.

5.39 There was a statistically non-significant excess risk of neonatal death in comparison with national rates in the offspring of Swedish women treated for skin haemangioma in childhood (Källén et al, 1998). The frequency of total perinatal mortality (neonatal death and stillbirth) did not differ significantly between ovarian dose categories.

5.40 We believe that the epidemiological studies provides no significant evidence that there is a link between parental preconceptional irradiation and neonatal death.

Congenital abnormalities

Laboratory studies of congenital abnormalities

5.41 We have noted in Chapter 3 that for a variety of reasons rodent models are not suitable for the examination of stillbirth or miscarriage following exposure to ionising radiation. However, animal models have provided a considerable body of information on the induction of congenital abnormalities following parental radiation, which is relevant to this report.

5.42 Studies with mice have shown that germ cell irradiation can induce significant levels of abnormality in the fetus. The incidence of these effects varies with the radiation dose, whether the germ cell was male or female, the stage of the germ cell at the time of irradiation, and the time between irradiation and the assessment of damage. However, in spite of uncertainties, mouse genetic data support the view that ionising radiation can induce dominant mutations in the germ line, which are expressed as congenital abnormalities in offspring. Some of the congenital abnormalities induced in mice are neural tube defects. These fall into the same general category as those reported in two epidemiological studies on the offspring of male radiation workers occupationally exposed to low radiation doses, and also a study of the offspring of women exposed for medical reasons in childhood.

5.43 In mouse studies conducted under carefully controlled laboratory conditions the presence of pre-existing susceptibility and/or environmental factors may be a cause of the different background rates of congenital abnormality. As described in Chapter 3, these factors would be expected to be far more difficult to take into account in studies on possible effects of germ line irradiation of human populations which are characterised by great genetic diversity.

5.44 Quantification of the mouse germ line effects has not been straight-forward, largely because of the variation in background rates. However, a genetic doubling dose of around 3 Gy for chronic low LET radiation has been estimated for male germ cells, although with substantial uncertainty (between 2 and 5 Gy). These studies also draw attention to the problems of establishing a baseline rate of congenital abnormality in studies on radiation effects in human populations. Furthermore, effects resulting from irradiation of mouse spermatogonia (that might be relevant to pregnancy outcome in humans) have been reported, including defects in cell proliferation and fertilisation, and instability at repeat DNA sequences. None of these effects is explicable in terms of conventional mutational events.

5.45 In addition to the data on classical radiation mutational damage resulting in congenital abnormality, there is increasing evidence that other, much more subtle, effects (such as hypersensitivity of repeat sequences in chromosomes and changes in gene expression) might be of importance in evaluating possible adverse reproductive outcomes following exposure to ionising radiation (see paragraphs 2.4–2.7). These are complemented by reports of persisting differences in the cells of the offspring of irradiated fathers that do not involve conventional mutational mechanisms. The differences include reduced growth

rate, altered sensitivity to radiation and cyclophosphamide and, in the case of sperm, altered fertilisation ability (see paragraphs 3.9–3.11). However, although a considerable amount of work is underway to try to understand some of the effects, the amount of data currently available is still quite small. It is not possible, at present, to say whether these effects will have any health implications or, if they do, how large these health consequences might be.

Epidemiological studies of all congenital abnormalities taken together

5.46 Several epidemiological studies have reported findings relevant to the question of whether exposure to radiation leads to congenital malformations in the offspring of the irradiated persons. The evidence from the various studies is discussed and then summarised. We will first consider all congenital abnormalities taken together and then the specific grouping of neural tube defects.

5.47 Investigations of congenital abnormality have been undertaken in the atomic-bomb survivors. Otake et al (1990) reported a statistically non-significant positive trend of risk of congenital malformation with parental conjoint gonadal dose. An earlier investigation (Schull et al, 1981), using less reliable dose estimates, considered the effects of irradiation of men and of women separately. It found a statistically non-significant positive trend with paternal gonadal dose and a statistically non-significant negative trend with maternal gonadal dose.

5.48 In the Cumbrian study by Parker et al (1999), the causes of stillbirths were available from 1961. Congenital abnormalities were considered in the cohort analysis, but not in the case–control analysis. Within the cohort study analyses were performed for all stillbirths deemed to be due to congenital disorders and for the subset of neural tube defects. For the former, a trend with dose was observed which achieved statistical significance (RR = 1.43 per 100 mSv, CI 0.93–1.94, one-sided $p = 0.047$).

5.49 The Nuclear Industry Family Study (NIFS) (Doyle et al, 2000) found no firm evidence of a link between radiation work and congenital abnormalities in offspring. In the children of monitored men, there was no increase in the occurrence of all major malformations taken together, nor were risks significantly elevated for any of the diagnostic groupings. There were no significantly raised risks in the children of monitored mothers. However, while most relative risks were above unity the authors noted that the numbers were small. There was no evidence for any trend in the rate of congenital abnormalities with radiation dose.

5.50 In the study by Sever et al (1988a), there was no excess of major groups of malformations in the offspring of workers at the Hanford plant. There has been no suggestion from other studies that the two conditions which were reported in excess (dislocation of the hip and tracheoesophageal fistula) were due to anything other than chance.

5.51 With the exception of neural tube defects (see below), there was no evidence for an association between parental preconceptional irradiation and any of the health endpoints in the case–control study of Sever et al. In particular, there was no trend with parental preconceptional dose for the category ‘all major malformations’.

5.52 There was a slight excess of congenital malformations in the offspring of a group of Swedish women treated for skin haemangioma in childhood, but there was no trend of malformation risk with ovarian preconceptional dose (Källén et al, 1998).

5.53 In the Canadian case–control study of congenital abnormalities (Green et al, 1997) there was no evidence for an increase in the risk of congenital abnormalities in the offspring of radiation workers. Nor was there evidence for an increased risk in the children of fathers with recorded preconceptional dose, whether for all congenital abnormalities or in the four subgroups considered. No analysis by preconceptional dose category was carried out. Too few mothers had recorded doses for an analysis to be possible.

5.54 There was no association of the risk of three groups of congenital malformations with paternal preconceptional gonadal dose or with paternal work in uranium mines in the offspring of a Navajo cohort (Shields et al, 1992). However, there were some indications of excess risk for mothers living near a uranium mine or mill. These findings are based on a fairly large number of cases (228 congenital malformations excluding stillbirths) but the nature of the study did not allow a test for trend with dose.

5.55 There was no statistically significantly elevated risk of major congenital abnormalities in the offspring of a cohort of female radiographers in the UK (Roman et al, 1996), although there was no information on parental preconceptional dose in this study. The number of cases born to fathers was small (23) and so the study was uninformative on any risk following irradiation of fathers.

5.56 We note that in a study of newborns from areas along the Kerala coast (India), with different levels of natural radiation, no association was found between the incidence of congenital malformations and areas with different average radiation levels (Jaikrishnan et al, 1999).

5.57 In addition to the papers we have quoted, there are several published studies of pregnancy outcomes among female cancer survivors and the partners of male cancer survivors. For example, we have described studies involving up to 5000 survivors of childhood/adolescent cancer (Byrne et al, 1998). This reported no evidence of excess heritable damage including stillbirth and congenital malformation in offspring.

5.58 However, the results of such studies are difficult to interpret because of the known associations between cancer and congenital abnormalities: there is likely be some inherent tendency for these conditions to occur in the children of survivors irrespective of the radiation exposure of the parents. Moreover, many of these patients also receive potentially mutagenic chemotherapy. Thus positive findings in this group could not with certainty be ascribed to radiation. Negative findings can provide only very limited evidence that preconceptional irradiation does not increase the risk of adverse outcomes, since there is at present only very limited information on the gonadal doses received by these patients and we have no idea of the statistical power of these studies. Thus, negative findings must be interpreted with great caution.

5.59 There is, however, one large study in progress with good dosimetry (Boice et al, 2000), and the results of that study will provide good information relevant to the questions discussed here.

Does radiation cause congenital abnormalities in humans?

5.60 There are difficulties in studying these relatively rare outcomes, where statistical power is likely to be low. It may also be difficult to establish a control population against which the absolute frequency of abnormalities can be compared; a particular problem may be differences in methods of ascertainment in exposed and reference populations. Differences in the definition of what constitutes a congenital abnormality may also complicate comparisons between studies.

5.61 If there were a radiation-induced excess of a particular endpoint one might expect an absolute excess compared to the control population and also that rates were positively correlated in some way with radiation dose. Given the difficulties, we must consider the possibility that a genuine effect may not manifest both these characteristics. In particular, if there are few individuals in the high dose categories, the induced cases may be too few to generate a significant overall excess.

5.62 Of course, no weight should be given to the lack of evidence from studies which do not have sufficient power to distinguish an effect of the size postulated.

5.63 Several studies offer some evidence on the possible induction of congenital abnormalities (of all kinds) by irradiation of fathers. However, no clear picture emerges. It is our judgement that the epidemiological evidence suggests that an association of this kind, if it exists, is likely to be concentrated in the specific subgrouping of neural tube defects which we consider below.

5.64 There is even less information on the possible induction of congenital abnormalities in the offspring of irradiated mothers. Evidence from the survivors of the atomic bombings is equivocal. That from the radiographers study is negative, but relates to a very low dose population. The NIFS found no significant effects, although odds ratios tended to be above unity. The study of the offspring of Swedish haemangioma patients involved some high dose patients; it found some evidence of an absolute excess, but no trend with dose. From this limited evidence it is impossible to conclude that irradiation of mothers leads to congenital abnormalities in their children, but the possibility cannot be conclusively rejected.

5.65 We do not believe that the evidence supports the idea that a detectable increase in congenital abnormalities in general has resulted from parents' exposure to ionising radiation, in the studies that have been reviewed.

Congenital abnormalities – neural tube defects

5.66 We have concluded above that the balance of the evidence does not support the idea that there is an association between radiation exposure of parents and congenital abnormalities in their children. However, one sub-grouping of congenital abnormalities, neural tube defects, deserves more careful examination. An outline of the nature of neural tube defects is given in Box 4.

5.67 In the Cumbrian cohort study by Parker et al (1999), the causes of stillbirths were available from 1961. Analyses were performed for all stillbirths deemed to be due to congenital disorders and for the subset of neural tube defects. For the former, a trend with dose was observed which just achieved statistical significance (RR = 1.43 per 100 mSv, CI 0.93–1.94, one-sided $p = 0.047$). The trend was more marked and statistically significant in stillbirths due to neural tube defects where the relative risk was 1.69 per 100 mSv (CI 1.10–2.32, $p = 0.011$).

5.68 The Nuclear Industry Family Study (NIFS) (Doyle et al, 2000) found no firm evidence of a link between radiation work by fathers and neural tube defects. There was no suggestion of a raised risk of abnormalities of the central nervous system in the children of monitored mothers.

5.69 The discrepancy between the Cumbrian study and the NIFS appears to be puzzling, because there is significant overlap between the study populations. We are unable to identify the reason for this difference, although a number of possibilities have been mentioned.

Box 4 What are neural tube defects?

Neural tube defects are major malformations of the central nervous system in which the central canal of the malformed brain or spinal cord is persistently open to the outside environment. During intrauterine development, the exposed nervous tissue degenerates leading either to absence of the cranial vault and a severely damaged brain, as in anencephalus, or to local disruption of the vertebrae and spinal nerve pathways, as in spina bifida (Copp et al, 1990). Most infants with anencephalus are stillborn, although as the brain stem including the respiratory centres may be intact, live-born infants may survive for a few days or so (Elwood et al, 1992).

Spina bifida is a general term describing the many varieties of lesions due to the midline separation of the vertebrae. The proportion of cases of spina bifida which are stillborn exhibits marked variations (Little, 1992; EUROCAT Working Group, 1997). The prognosis for live-born infants with spina bifida varies considerably worldwide, depending not only on the severity of the lesion but also on factors such as the availability, use, and acceptance of medical and surgical treatment (Botto et al, 1999).

In addition to anencephalus and spina bifida, which are the most investigated types, neural tube defects also include a number of rarer conditions (Elwood et al, 1992).

5.70 We noted in our Seventh Report that an apparent conflict between the NIFS and the Record Linkage Study (Draper et al, 1997) was resolved by a detailed intercomparison which showed that the overlap in study populations was much smaller than had first been supposed. The two studies could, in fact, be regarded as almost independent. An intercomparison between the Cumbrian study and the NIFS might also be instructive.

5.71 In the study by Sever et al (1988a), there was no excess of neural tube defects in the offspring of workers at the Hanford plant. However, while Sever et al found no absolute excess of congenital abnormalities, they reported a statistically significant ($p = 0.04$) positive trend of neural tube defects with paternal preconceptional dose in the offspring of Hanford workers for births in the period 1957–1980. This trend is based on only 11 cases, and the authors were unsure as to the interpretation of the finding. Sever et al interpreted their result as due to chance, but in view of the similar finding of Parker et al, we feel this interpretation should not be regarded as conclusive.

5.72 Numbers were too small for an analysis of specific malformations by maternal preconceptional dose. However, an analysis by conjoint parental dose is presented for certain malformations. For neural tube defects this includes an extra case compared to the analysis of paternal exposure and the trend with dose is somewhat more significant.

5.73 In a related study of the prevalence of congenital abnormalities near the Hanford plant, Sever et al (1988b) observed a significant overall excess of neural tube defects, for births over the period 1968–1980. However, Sever et al concluded that the observed excess (17 cases in a total of 40) was unlikely to be explained by occupational exposure to ionising radiation:

(i) reanalysis of the case–control study for the period 1968–1980 did not show a correlation between neural tube defects and radiation exposure of the parents,

(ii) only seven of the cases of neural tube defects had a parent who worked at Hanford before the infant was conceived.

5.74 Källén et al (1998) studied the offspring of a group of Swedish women treated for skin haemangioma in childhood. There was a statistically significant ($p = 0.02$) positive trend of neural tube defects with ovarian preconceptional dose in this study, but there was no overall excess prevalence at birth. The authors suggested that the positive trend with dose for neural tube defects

might be a result of multiple significance testing. We will consider it in the context of other studies.

5.75 The Canadian case–control study of congenital abnormalities in the offspring of radiation workers (Green et al, 1997) found no evidence for an increase in the risk of abnormalities of the neural system. Neural tube defects were not considered as a separate category.

5.76 Investigations of congenital abnormality in the atomic-bomb survivors did not consider neural tube defects separately.

5.77 There was no association of the risk of congenital malformations with paternal preconceptional gonadal dose or with paternal work in uranium mines in the offspring of a Navajo cohort (Shields et al, 1992). However, neural tube defects were not considered as a separate category.

5.78 The study of the offspring of medical radiographers in the UK (Roman et al, 1996) did not consider neural tube defects separately. It contained too few men to give useful information on possible effects of male irradiation.

5.79 The study of the offspring of cancer survivors who had received mutagenic radiation and/or chemotherapy treatment prior to conception of their children did not find any evidence of excess neural tube defects (Byrne et al, 1998; Byrne, 1999). However, we have noted the difficulties in interpreting such studies.

Does radiation cause neural tube defects in humans?

5.80 We have noted above the difficulties in studying all congenital abnormalities taken together. All the considerations apply, with equal or greater force, to neural tube defects. There is a particular problem in evaluating the evidence on an association between the latter and preconceptional irradiation. This is the weight that should be given to studies which did not consider neural tube defects as a separate category, but which considered some wider grouping or else all congenital abnormalities together. Suggestive positive findings from such studies may be driven by a larger effect in a subgroup of abnormalities. Conversely, a negative finding limits the possible size of an effect in such a subgroup, although this may be hard to quantify. In the former case, investigators may go on to consider subcategories of abnormality, but this is less likely if they find an overall deficit.

5.81 Neural tube defects are particularly difficult to study because of factors which mean that their prevalence is changing markedly with time. These include differences in methods of ascertainment and environmental/lifetime factors including diet and folic acid supplementation in the peri-conceptional period. The increase in prenatal diagnosis may affect the frequency of elective abortion and thus reduce the number of infants born with these defects.

5.82 It is thought that non-genetic factors are generally more important than heritable genetic variables in the induction of neural tube defects (see Box 5). The majority of neural tube defects are normally related to maternal or environmental factors – in particular, maternal diets low in folate (MRC, 1991) – and are not associated with paternal influences (Elwood et al, 1992). It is very likely that variations in these factors lie behind, for example, the strong temporal trends in the incidence of stillbirths within the Cumbrian study of Parker et al (1999). Similarly, socioeconomic gradients are observed in this and other cohorts (ONS, 1998; Parker et al, 1999). These considerations do not rule out the possibility of a link between parental preconceptional irradiation and neural tube defects, but they do warn that there is considerable potential for bias or confounding.

Box 5 What is known about neural tube defects?

Geographical variation in the prevalence at birth of neural tube defects is striking. The interpretation of data since around 1980 is complicated by the fact that in many areas of the world the use of antenatal diagnosis and selective abortion has become frequent either for high risk mothers or based on screening all pregnant women, and the effects of this on recorded frequencies at birth are not easy to document (Little and Elwood, 1992a). Without adjustment for the effects of selective termination of pregnancy, the prevalence at birth of these defects in the 1980s was around 1–2 per 1000 births in most of the British Isles, and in some other countries. These rates compare with frequencies of around 1–2 per 1000 for Down's syndrome, and about 0.2 per 1000 for the incidence of all cancers in the first year of life (Parkin et al, 1988).

The British Isles have been an area of relatively high risk. In the late 1980s and early 1990s, the rates for anencephalus and spina bifida combined were between 3 and 6 per 1000 births, in contrast to rates of 6 to 10 per 1000 births some 20 years earlier. While a substantial proportion of this decrease is due to antenatal screening, it seems clear that this is not the whole explanation and that there has been a considerable natural decline. The pattern recognised in the 1950s of a major trend from high rates in Scotland and Ireland to low rates in the Midlands and South East of England still persists. In England and Wales, on the basis of the national congenital malformation notification system and information on pregnancies terminated because the fetus had a neural tube defect, the rates of decline have stabilised since 1992 (Kadir et al, 1999). Apart from the effects of antenatal diagnosis, the most commonly suggested reason for the declining trend is that maternal diet is likely to have improved. This hypothesis lacks empirical evidence either to support or to refute it (Elwood et al, 1992) and it cannot be assumed that the diseases will disappear spontaneously.

A higher rate of neural tube defects in the lower socioeconomic groups has been recorded in the UK and several other countries (Little and Elwood, 1992b). It is not clear whether this has persisted or has diminished in recent years.

The most intensely investigated exposure has been diet during pregnancy. Secular and seasonal variation, and variation by social class, are the features most readily attributed to a dietary cause (Elwood et al, 1992). Most dietary hypotheses have not attempted to explain other features of the epidemiology of these two effects, such as the variations by ethnic group, maternal parity, or the sex of the infant. In particular, insufficient folic acid during pregnancy has been shown to increase the risk of neural tube defects substantially. Supplements are now given in many countries.

5.83 The Parker et al study reported a significant correlation between stillbirths due to neural tube defects and paternal radiation exposure. A broadly similar observation had been made by Sever et al (1988b) for workers at the Hanford plant in the USA. Sever et al also found elevated levels of neural tube defects in the area around Hanford, although these did not appear to be due to the influence of Hanford workers.

5.84 Against this, there is no evidence for increased levels of neural tube defects in the NIFS. Investigations of the group of all congenital abnormalities in the atomic-bomb survivors provide no firm evidence of a radiation-related risk (neural tube defects were not studied alone). The Canadian case–control study (Green et al, 1997) found no evidence for increased congenital abnormality in men with a non-zero preconceptional dose. It did not consider neural tube defects as a separate category or undertake a test for trend with dose. Studies of the offspring of cancer survivors must be interpreted with caution, but we note that large studies of this type have failed to find an association.

5.85 Two independent studies have provided evidence for increased rates of neural tube defects in the offspring of more highly irradiated men than in those receiving lower doses. Animal experiments also suggest that neural tube defects may be a consequence of paternal irradiation, albeit at significantly higher doses than those seen in the human epidemiology. Other epidemiological studies have failed to find such an association. We are not fully convinced that such an association is real, but the possibility remains. If a causal relationship exists the evidence suggests that lifetime exposure is the dosimetric quantity of relevance rather than the dose in a short period before conception.

5.86 There is far less information on the possible induction of neural tube defects in the offspring of women.

5.87 Källén et al, in their 1998 study of the offspring of women who had been irradiated in infancy, found a statistically significant association between neural tube defects and ovarian preconceptional dose, although overall levels of neural tube defects were not elevated.

5.88 Many fewer women than men work in the nuclear industry and they tend to receive much lower doses. However, the NIFS found no evidence for increased central nervous system abnormalities in the offspring of monitored mothers.

5.89 The radiographers study (Roman et al, 1996) was large but involved low dose individuals. It did not find an excess of congenital abnormalities in the offspring of female radiographers, although doses were small.

5.90 We believe that there is not nearly enough evidence to regard a link between irradiation of women and neural tube defects in their offspring as established.

Sex ratio studies

5.91 Chapter 4 also describes some studies in which the ratio of boys to girls in the children of irradiated parents has been investigated. The sex of a baby is, of course, determined by whether it has two X chromosomes (a girl) or one X and one Y (a boy).

5.92 The Y chromosome contains much less genetic information than the X chromosome. Whether fathers or mothers are irradiated, it is therefore damage to the X chromosome which is more important. If a daughter receives a damaged X chromosome from either her father or her mother, she is likely to have an intact copy of the genes concerned on the X chromosome from her other parent. Boys, however, have only one X chromosome, from their mother. If this is damaged the Y chromosome is unlikely to be able to compensate. Thus sons would display the consequences of both X-linked dominant and recessive mutations; daughters, only the former.

5.93 Therefore, irradiation of parents could result in a deficit of male births.

5.94 The UNSCEAR (1993) report discusses the likely effects of irradiation on the ratio of the sexes of offspring. On the basis of such considerations as those in the preceding paragraphs, it concluded that the most pertinent evidence would come from a case in which mothers were exposed and fathers were unexposed. UNSCEAR noted that the evidence from the atomic-bomb survivors showed no such effect, although it has been seen in the offspring of patients receiving radiotherapy.

5.95 An excess of male offspring was seen by Parker et al (1999) in the children of men who had worked at any time (either before or after conception of the child) at Sellafield. A somewhat larger effect is seen in the children of men who had received an estimated 90-day preconceptional dose over 10 mSv. However, three preconceptional dose categories were examined so this was not a prior hypothesis and its interpretation is difficult.

5.96 No disturbance of the sex ratio was seen in the NIFS (Maconochie et al, 2001). Nor was there any trend with total preconceptional dose. No test for trend with dose in the three months before conception was carried out. Nor was there any change in the sex ratio of children born to the survivors of childhood cancer (Byrne et al, 1998).

5.97 There was some evidence for an increased proportion of boys born to the most highly exposed group of women who had been treated with radiation for haemangioma (Källén et al, 1998). These women had received ovarian doses above 500 mGy. However, the numbers were small (69 versus 53) and the result was not statistically significant.

5.98 The evidence is scanty and conflicting. If there were any effect of parental irradiation on the sex ratio of their offspring, it would be expected to be different in the case of irradiation of fathers and of mothers. In either case, there is no obvious mechanism to account for an excess of male children and we cannot regard the evidence as convincing without independent confirmation.

Summary

5.99 In principle, epidemiological studies cut through many of the difficulties in extrapolating laboratory studies to possible effects in human populations. However, epidemiological studies have problems of their own, particularly in allowing for confounding factors and the effects of chance. In addition, almost all the published literature on pregnancy outcome following parental exposure to radiation suffers from a lack of statistical power due to the relatively low doses that were experienced compared to those used in animal experiments. It must be realised that failure to find significant effects in epidemiological studies does not imply that such effects might not be observed with higher doses.

5.100 There is no significant evidence from the few published studies that irradiation of either fathers or mothers results in adverse reproductive outcomes in general. If such deleterious effects do occur, we judge that they would be seen more clearly in studies of specific endpoints.

5.101 The limited data provide no significant evidence that miscarriage is a result of parental irradiation.

5.102 Considerable uncertainties remain as to whether there is a relationship between paternal preconceptional irradiation and stillbirth. We certainly do not regard such a link as established, but neither can we entirely rule it out. There is less information relating to a possible link between maternal irradiation and stillbirth, but we regard the evidence for such an association as weak.

5.103 We believe that there is no significant evidence that there is a link between parental preconceptional irradiation and neonatal death.

5.104 Several studies offer some evidence on the possible induction of congenital abnormalities (of all kinds) by irradiation of fathers. Again, there is less information concerning women. It is our judgement that an association of this kind, if it exists, is likely to be concentrated in the specific subgrouping of neural tube defects.

5.105 We are not fully convinced that the available data prove there is an association between paternal preconceptional irradiation and neural tube defects, but the possibility remains. If a causal relationship exists, the evidence suggests that lifetime exposure is the dosimetric quantity of relevance rather than the dose in a short period before conception. We believe that there is not nearly enough evidence to regard a link between irradiation of women and neural tube defects in their offspring as established.

5.106 In principle, irradiation of parents might result in a deficit of male children. However, such evidence as there is tends to be for an excess. There is no mechanism to account for such an observation, and we cannot regard the evidence as supporting a causal link without independent confirmation.

CHAPTER 6

CONCLUSIONS

6.1 Animal studies clearly show that irradiation of germ cells at high doses leads to dominant lethal mutation and congenital abnormalities. However, it is apparent that the available epidemiological data are inadequate to allow definitive statements about the effect of preconceptional radiation exposure on pregnancy outcomes. In part this is due to the difficulties in obtaining reliable figures for the endpoints of concern. A further possibility is that the exposures in most of the studies may have been too low to produce a detectable effect. We note that the only British study to report a statistically significant dose-dependent effect of paternal preconceptional irradiation on stillbirth frequency was of a workforce (the Sellafield workforce) which in its early years included workers who experienced occupational doses larger than those in most other groups studied. Moreover, the effect reported was dominated by stillborn offspring of those workers who received the highest preconceptional doses.

6.2 From all the epidemiological data we have examined, we have concluded that there is little significant evidence that adverse reproductive outcomes in general are related to parental exposure. Similarly, the limited data available do not link miscarriage or neonatal death with parental irradiation. The evidence from sex ratio studies is so scanty and conflicting that it is hard to draw conclusions regarding an association with irradiation of fathers and mothers. Almost all of the published studies on pregnancy outcome following parental exposure to radiation in human populations lack statistical power. This is due to the low doses to which these human populations were exposed, as compared to the much higher doses used in animal experiments. It must be realised that failure to find significant effects in epidemiological studies does not imply that such effects might not be observed in humans at higher dose levels.

6.3 We have also examined the data relating to congenital abnormalities in the offspring of irradiated parents. We conclude that, in the studies reviewed, the evidence does not support a link between congenital abnormalities in general and parental exposure to radiation. It is our judgement that if an association of this kind exists, at past environmental or occupational doses, it is likely to be concentrated in the specific subgroup of neural tube defects. Two independent studies have provided evidence for increased rates of neural tube defects in the children of men irradiated occupationally (in the higher dose range). There is not enough evidence to provide a link between radiation and neural tube defects in the children of irradiated women. We have also noted that some of the congenital abnormalities (neural tube defects) induced in mice fall into the same general category as those reported in two epidemiological studies. Animal data show that neural tube defects can be initiated by irradiation of the parents, although this occurred at very much higher doses of radiation than have been received by radiation workers.

6.4 We are unable to identify any other group within the UK that could be used to confirm or refute the effect observed in the Sellafield workforce. We

are, therefore, not making any recommendation for further epidemiological work in this area. The only population that might be informative appears to be the workforce at the Mayak radiochemical plant in Russia. The cohort consists of almost 19,000 workers, of whom over 500 have recorded gamma-ray doses of over 4 Gy, with a further 1700 workers exceeding 2 Gy (Koshurnikova et al, 1999). It is likely that pregnancy outcome data exist among the medical records of these workers, but we are not aware of any plans to study reproductive outcome or other outcomes (such as cancer) in their children.

6.5 Overall, we do not expect that current occupational exposures will lead to a detectable increase in risk of any of the major reproductive anomalies for which we have data, such as miscarriage, stillbirth, neonatal death, or congenital malformation. If there was an increased risk arising from exposures in the early years of the nuclear industry when exposures were higher, then this risk has not been established in the totality of available studies, either in the UK or overseas.

6.6 The available studies on reproductive outcome, whether they are in rodents or in humans, have focused on fairly gross effects and these have been interpreted on the basis of conventional genetic mechanisms, such as the induction of gene mutations, small deletions and chromosomal aberrations. This is partly because methods for measuring subtle effects have not been available and is in any case not unreasonable since these major effects are those which would cause most concern. Our conclusions are necessarily based on such published information. We are aware, however, of reports that the cells of the offspring of rodents exposed to high doses of radiation are abnormal in several respects. We are also aware that changes in gene expression have been reported in the descendants of irradiated mice (Baulch et al, 2001; Nomura, 2001). Such changes in gene expression could in principle cause subtle cellular changes during embryonic development, eg growth rate. While there is no evidence that such changes would have consequences for health, this possibility should not be discounted. It is known that various factors, mainly nutritional, operating during pregnancy are associated with a number of diseases in later life, including coronary heart disease, stroke, diabetes and hypertension (Barker, 2001) and these are presumably mediated by changes in gene expression. However, if there are radiation-induced changes in gene expression in the embryo following parental germ cell exposure, the consequences might well fall within the normal range of phenotypic variability of the human population and would certainly be very difficult to distinguish in epidemiological studies. Nevertheless, subtle effects which fall within the range of normal variability that exists among healthy people may still have public health consequences.

CHAPTER 7

RECOMMENDATIONS

Recommendation 1

We are unable to identify any UK population that could be usefully used to clarify the uncertainties that we have discussed in Chapter 5 so we make no recommendation for further epidemiological work in this area.

Recommendation 2

We note that in epidemiological studies of pregnancy outcome it has hitherto been feasible to examine only gross effects such as miscarriage, stillbirth and malformation. We note that recent work with mice suggests the possibility that there may be more subtle effects, such as epigenetic effects, that have not so far been considered. COMARE has undertaken to monitor developments in this area of research with a view to assessing the implications for human health.

REFERENCES

Abrahamson A and Tawn E J (2001). Risk of stillbirth in offspring of men exposed to ionising radiation. *J Radiol Prot,* **21**, 133–44.

Alberman E, Botting B, Blatchley N and Twidell A (1994). A new hierarchical classification of causes of infant deaths in England and Wales. *Arch Dis Childhood,* **70**, 403–9.

Barker D J (2001). A new model for the origins of chronic disease. *Med Health Care Philos*, **4**(1), 31–5.

Bartlett D T (1982). A review of Japanese bomb dosimetry. *Radiat Prot Dosim,* **2**, 127–39.

Baulch J E, Raabe O G and Wiley L M (2001). Heritable effects of paternal irradiation in mice on signalling protein kinase activities in F3 offspring. *Mutagenesis,* **16**(1), 17–23.

Baulch J E, Raabe O G, Wiley L M and Overstreet J W (2002). Germline drift in chimeric male mice possessing an F2 component with a paternal F0 radiation history. *Mutagenesis,* **17**(1), 9–13.

Berber R, Plumb M A, Boulton E, Roux I and Dubrova Y E (2202). Elevated mutation rates in the germ line of first- and second-generation offspring of irradiated male mice. *Proc Natl Acad Sci USA,* **99**, 6877–82.

Black D (1984). Investigation of the possible increased incidence of cancer in West Cumbria. Report of the Independent Advisory Group. London, HMSO.

Boice J D, Robison L L, Mertens A, Stovall M, Green D M and Mulvihull J J (2000). Stillbirths and male irradiation. *J Radiol Prot,* **20**, 321–4.

Botto L D, Moore C A, Khoury M J and Erickson J D (1999). Neural-tube defects. *N Engl J Med,* **341**, 1509–19.

Bradford Hill A (1965). The environment and disease: association or causation. *Proc Roy Soc Med,* **58**, 295–300.

Bridges B A (2001). Radiation and germline mutation at repeat sequences: are we in the middle of a paradigm shift? *Radiat Res,* **156**(5 Part 2), 631–41.

Burruel V R, Raabe O G and Wiley L M (1997). *In vitro* fertilization rate of mouse oocytes with spermatozoa from the F1 offspring of males irradiated with 1.0 Gy ^{137}Cs gamma-rays. *Mutat Res,* **381**(1), 59–66.

Byrne J (1999). Long-term genetic and reproductive effects of ionizing radiation and chemotherapeutic agents on cancer patients and their offspring. *Teratology,* **59**, 210–15.

Byrne J, Rasmussen S A, Steinhorn S C, Connelly R R, Myers M H, Lynch C F, Flannery J, Austin D F, Holmes F F, Holmes G E, Strong L C and Mulvihill J J (1998). Genetic disease in offspring of long-term survivors of childhood and adolescent cancer. *Am J Hum Genet,* **62**, 45–52.

Carls N and Schiestl R H (1999). Effect of ionizing radiation on trans-generational appearance of p(un) reversions in mice. *Carcinogenesis*, **20**(12), 2351–4.

Cattanach B M, Burtenshaw M D, Rasberry C and Evans E P (1993). Large deletions and other gross forms of chromosome imbalance compatible with viability and fertility in the mouse. *Nat Genet,* **3**(1), 56–61.

Cattanach B M, Evans, E P and Raspberry C (1995a). Incidence and distribution of radiation-induced large deletions in the mouse. IN *Radiation Research 1895–1995,* Proceedings 10th International Congress on Radiation Research, Wurzburg, pp 531–4 (U E A Hagen, ed).

Cattanach B M, Patrick G, Papworth D, Goodhead D T, Hacker T, Cobb L and Whitehill E (1995b). Investigation of lung tumour induction in BALB/cJ mice following paternal X-irradiation. *J Radiat Biol,* **67**(5), 607–15.

Committee on the Medical Aspects of Radiation in the Environment (COMARE) (1988). Second Report. Investigation of the possible increased incidence of leukaemia in young people near the Dounreay Nuclear Establishment, Caithness, Scotland. London, HMSO.

Committee on the Medical Aspects of Radiation in the Environment (COMARE) (1989). Third Report. Report on the incidence of childhood cancer in the West Berkshire and North Hampshire area, in which are situated the Atomic Weapons Research Establishment, Aldermaston and the Royal Ordnance Factory, Burghfield. London, HMSO.

Committee on Medical Aspects of Radiation in the Environment (COMARE) (2002). Seventh Report. Parents occupationally exposed to radiation prior to the conception of their children. A review of the evidence concerning the incidence of cancer in their children. Chilton, NRPB.

Committee on Medical Aspects of Radiation in the Environment (COMARE) (2004). Table summarising epidemiological studies of birth outcomes. Available on the COMARE website: www.comare.org.uk.

Copp A J, Brook F A, Estibeiro P, Shum A S W and Cockroft D L (1990). The embryonic development of mammalian neural tube defects. *Prog Neurobiol,* **35**, 363–403.

Degteva M O, Shagina N B, Tolstykh E I, Vorobiova M I, Napier B A and Anspaugh L R (2002). Studies on the Techa River population: dosimetry. *Radiat Environ Biophys,* **41,** 41–4.

Dickinson H O, Parker L, Binks K, Wakeford R and Smith J (1996). The sex ratio of children in relation to paternal preconceptional radiation dose: a study in Cumbria, northern England. *J Epid Community Health,* **50**, 6454–652.

Doyle P, Maconochie N, Roman E, Davies G, Smith P G and Beral V (2000). Fetal death and congenital malformation in babies born to nuclear industry employees: report from the nuclear industry family study. *Lancet,* **356**, 1293–9.

Doyle P, Maconochie N and Roman E (2001a). Fetal death and radiation exposure. *Lancet,* **357**, 556–7.

Doyle P, Roman E, Maconochie N, Davies G, Smith P G and Beral V (2001b). Primary infertility in nuclear industry employees: report from the nuclear industry family study. *Occup Environ Med,* **58**, 535–9.

Draper G J, Little M P, Sorahan T, Kinlen L J, Bunch K J, Conquest A J, Kendall G M, Kneale G W, Lancashire R J, Muirhead C R, O'Connor C M and

Vincent T J (1997). Cancer in the offspring of radiation workers: a record linkage study. *Br Med J,* **315**, 1181–8.

Dubrova Y E, Plumb M, Gutierrez B, Boulton E and Jeffreys A J (2000a). Transgenerational mutation by radiation. *Nature,* **405**, 37.

Dubrova Y E, Plumb M, Brown J, Boulton E, Goodhead D, and Jeffreys A J (2000b). Induction of minisatellite mutations in the mouse germline by low-dose chronic exposure to gamma-radiation and fission neutrons. *Mutat Res,* **453**(1), 17–24.

Ehling U H (1966). Dominant mutations affecting the skeleton in offspring of X-irradiated male mice. *Genetics,* **51**, 1381–9.

Elwood J M, Little J and Elwood J H, Eds (1992). *Epidemiology and Control of Neural Tube Defects.* Oxford, Oxford University Press.

EUROCAT Working Group (1997). *Surveillance of Congenital Anomalies in Europe 1980–1994.* EUROCAT Report 7. Brussels, Scientific Institute of Public Health – Louis Pasteur.

Favor J (1989). Risk estimation based on germ-cell mutations in animals. *Genome,* **31,** 844–52.

Gardner M J, Snee M P, Hall A J, Powell C A, Downes S and Terrell J D (1990). Results of case–control study of leukaemia and lymphoma among young people near Sellafield nuclear plant in West Cumbria. *Br Med J,* **300,** 423–9.

Green L M, Dodds L, Miller A B, Tomkins D, Li J and Escobar M (1997). Risk of congenital anomalies in children of parents occupationally exposed to low level ionising radiation. *Occup Environ Med,* **54,** 629–35.

Holliday R (2001). Ageing and the biochemistry of life. *Trends Biochem Sci,* **26**(1), 68–71.

Hughes J S (1999). Ionising radiation exposure of the UK population: 1999 review. Chilton, NRPB-R311.

Jaikrishan G, Andrews V J, Thampi M V, Koya P K M, Rajan V K and Chauhan P S (1999). Genetic monitoring of the human population from the high-level natural radiation areas of Kerala on the southwest coast of India. I. Prevalence of congenital abnormalities in newborns. *Radiat Res,* **152**, 149–53.

Kadir R A, Sabin C, Whitlow B, Brockbank E and Economides D (1999). Neural tube defects and periconceptional folic acid in England and Wales: retrospective study. *Br Med J,* **319**, 92–3.

Källén B, Karlsson P, Lundell M, Wallgren A and Holm L-E (1998). Outcome of reproduction in women irradiated for skin hemangioma in infancy. *Radiat Res,* **149,** 202–8.

Kiaris H, Ergazaki M and Spandidos DA (1995). Instability at the H-ras minisatellite is associated with the spontaneous abortion of the embryo. *Biochem Biophys Res Commun,* **214**(3),788–92.

Kirk K M and Lyon M F (1982). Induction of congenital anomalies in offspring of female mice exposed to varying doses of X-rays. *Mutat Res,* **106**(1), 73–83.

Kirk K M and Lyon M F (1984). Induction of congenital malformations in the offspring of male mice treated with X-rays at pre-meiotic and post-meiotic stages. *Mutat Res,* **125**, 75–85.

Koshurnikova N A, Shilnikova N S, Okatenko P V, Kreslov V V, Bolotnikova M G, Sokolnikiva M E, Khokhriakov V F, Suslova K G, Vassilenko E K and Romanov S A (1999). Characteristics of the cohort of workers at the Mayak nuclear complex. *Radiat Res,* **152,** 352–63.

Kossenko M M and Degteva M O (1994). Cancer mortality and radiation risk evaluation for the Techa river population. *Sci Total Environ,* **142,** 73–89.

Kossenko M M, Preston D L, Krestinina L Y, Degteva M O, Startsev N V, Thomas T, Vyushkova V P, Anspaugh L R, Napier B A, Kozheurov V P, Ron E and Akleyev A V (2002). Studies on the extended Techa river cohort: cancer risk estimation. *Radiat Environ Biophys,* **41,** 45–8.

Little J and Elwood J M (1992a). Geographical variation. IN *Epidemiology and Control of Neural Tube Defects*, pp 96–145 (J M Elwood et al, Eds). Oxford, Oxford University Press.

Little J and Elwood J H (1992b). Socio-economic status and occupation. IN *Epidemiology and Control of Neural Tube Defects*, pp 456–520 (J M Elwood et al, Eds). Oxford, Oxford University Press.

Little M P (1992). The risks of leukaemia and non-cancer mortality in the offspring of the Japanese bomb survivors and a comparison of leukaemia risks with those in the offspring of the Sellafield workforce. *J Radiol Prot,* **12**(4), 203–18.

Little M P (1999). A comparison of the risk of stillbirth associated with paternal pre-conception irradiation in the Sellafield workforce with that of stillbirth and untoward pregnancy outcome among Japanese atomic bomb survivors. *J Radiol Prot,* **19,** 361–73.

Luning K G, Frolen H and Nilsson A (1976). Genetic effects of ^{239}Pu salt injections in male mice. *Mutat Res,* **34**, 539–42.

Lyon M F and Renshaw R (1988). Induction of congenital malformation in mice by parental irradiation: transmission to later generations. *Mutat Res,* **198,** 277–83.

Macfarlane A and Mugford M (Eds) (2000). *Birth Counts: Statistics of Pregnancy and Childbirth,* Volumes 1 and 2. London, The Stationery Office.

Maconochie N, Roman E, Doyle P, Davies G, Smith P G and Beral V (2001). Sex ratio of nuclear industry employees' children. *Lancet,* **357,** 1589–91.

Medical Research Council (MRC) Vitamin Study Research Group (1991). Prevention of neural tube defects: results of the Medical Research Council Vitamin Study. *Lancet,* **338,** 131–7.

Morgan H D, Sutherland H G, Martin D I and Whitelaw E (1999). Epigenetic inheritance at the agouti locus in the mouse. *Nat Genet,* **23**(3), 314–18.

Muller W U, Streffer C, Wojcik A and Niedereichholz F (1999). Radiation-induced malformations after exposure of murine germ cells in various stages of spermatogenesis. *Mutat Res,* **425**(1), 99–106.

Neel J V and Schull W J (1991). *The Children of Atomic Bomb Survivors: A Genetic Study.* Washington DC, National Academy of Sciences.

Nomura T (1982). Parental exposure to X rays and chemicals induces heritable tumours and anomalies in mice. *Nature,* **296**, 575–7.

Nomura T (1988). X-ray and chemically induced germline mutation causing phenotypical anomalies in mice. *Mutat Res,* **198**, 309–20.

Nomura T (2001). Transgenerational teratogenesis and carcinogenesis by radiation and chemicals. *Mutat Res,* **483**(Suppl 1), S44.

Nikitina T V and Nazarenko S A (2000). Mutation in microsatellite repeats of DNA and embryonal death in humans. *Genetika,* **36**(7), 965–71.

Niwa O and Kominami R (2001). Untargeted mutation of the maternally derived mouse hypervariable minisatellite allele in F1 mice born to irradiated spermatozoa. *Proc Natl Acad Sci USA,* **98**(4), 1705–10.

Obasaju M F, Wiley L M, Oudiz D J, Miller L, Samuels S J, Chang R J and Overstreet J W (1988). An assay using embryo aggregation chimeras for the detection of nonlethal changes in X-irradiated mouse preimplantation embryos. *Radiat Res,* **113**(2), 289–99.

Office of National Statistics (ONS) (1998). *1996 Mortality Statistics*. Childhood, Infant and Perinatal Series DH3 No. 29. London, The Stationery Office.

Otake M, Schull W J and Neel J V (1990). Congenital malformations, stillbirths, and early mortality among the children of atomic bomb survivors: a reanalysis. *Radiat Res,* **122**, 1–11.

Parker L (2001). Fetal death and radiation exposure. *Lancet,* **357**, 556.

Parker L, Smith J, Dickinson H, Binks K, Scott L, McElvenny D, Jones S and Wakeford R (1997). The creation of a database of children of workers at a nuclear facility: an exercise in record linkage. *Appl Occup Environ Hyg,* **12**(1), 40–45.

Parker L, Pearce M S, Dickinson H O, Aitkin M and Craft A W (1999). Stillbirths among offspring of male radiation workers at Sellafield nuclear reprocessing plant. *Lancet,* **354**, 1407–14.

Parkin D M, Stiller C A, Draper G J and Bieber C A (1988). The international incidence of childhood cancer. *Int J Cancer,* **42**, 511–20.

Pearce M S, Dickinson H O, Aitkin M and Parker L (2002). Stillbirths among the offspring of male radiation workers at the Sellafield nuclear reprocessing plant: detailed results and statistical aspects. *J Roy Statist Soc A,* **165,** 523–48.

Peters J M, Tsark E C and Wiley L M (1996). Radiosensitive target in the mouse embryo chimera assay: implications that the target involves autocrine growth factor function. *Radiat Res,* **145**(6), 722–9.

Pils S, Muller W U and Streffer C (1999). Lethal and teratogenic effects in two successive generations of the HLG mouse strain after radiation exposure of zygotes – association with genomic instability? *Mutat Res,* **429**(1), 85–92.

Preston D L and Pierce D A (1988). The effects of changes in dosimetry on cancer mortality risk estimates in the atomic bomb survivors. *Radiat Res,* **114**, 437–66.

Rakyan V K, Chong S, Champ M E, Cuthbert P C, Morgan H D, Luu K V and Whitelaw E (2003). Transgenerational inheritance of epigenetic states at the murine Axin(Fu) allele occurs after maternal and paternal transmission. *Proc Natl Acad Sci USA,* **100**(5), 2538–43.

Roman E, Doyle P, Ansell P, Bull D and Beral V (1996). Health of children born to medical radiographers. *Occup Environ Med* **53,** 73–9.

Roman E, Doyle P, Maconochie N, Davies G, Smith P G and Beral V (1999). Cancer in children of nuclear industry employees: report on children aged under 25 years from nuclear industry family study. *Br Med J,* **318,** 1443–50.

Sankaranarayanan K (1999). Ionizing radiation and genetic risks. X. The potential 'disease phenotypes' of radiation-induced genetic damage in humans: perspectives from human molecular biology and radiation genetics. *Mutat Res,* **429**(1), 45–83.

Sankaranarayanan K (2001). Estimation of the hereditary risks of exposure to ionizing radiation: history, current status, and emerging perspectives. *Health Phys,* **80,** 363–9.

Sankaranarayanan K and Chakraborty R (2000). Ionizing radiation and genetic risks. XII. The concept of 'potential recoverability correction factor' (PRCF) and its use for predicting the risk of radiation-inducible genetic disease in human live births. *Mutat Res,* **453**, 129–81.

Schull W J, Otake M and Neel J V (1981). Hiroshima and Nagasaki: a reassessment of the mutagenic effect of exposure to ionizing radiation. IN *Population and Biological Aspects of Human Mutation* (E B Hook and I H Porter, Eds), pp 277–303. New York, Academic Press.

Searle A G and Beechey C (1986). The role of dominant visibles in mutagenicity testing. *Prog Clin Biol Res,* **209B**, 511–18.

Selby P B (1990). Experimental induction of dominant mutations in mammals by ionizing radiation. IN *Issues and Reviews in Teratology*, Volume **5,** pp 181–253 (H Kalter, Ed). New York, London, Plenum.

Selby P B and Selby P R (1977). Gamma-ray-induced dominant mutations hat cause skeletal abnormalities in mice. I. Plan, summary of results and discussion. *Mutat Res,* **43**, 357–75.

Selevan S G and Lemasters G K (1987). The dose–response fallacy in human reproductive studies of toxic exposures. *J Occup Med,* **29,** 451–4.

Sever L E, Gilbert E S, Hessol N A and McIntyre J M (1988a). A case–control study of congenital malformations and occupational exposure to low-level ionizing radiation. *Am J Epidemiol,* **127,** 226–42.

Sever L E, Hessol N A, Gilbert E S and McIntyre J M (1988b). The prevalence at birth of congenital malformations in communities near the Hanford site. *Am J Epidemiol,* **127,** 243–54.

Shields L M, Wiese W H, Skipper B J, Charley B and Benally L (1992). Navajo birth outcomes in the Shiprock uranium mining area. *Health Phys,* **63,** 542–51.

Shiraishi K, Shimura T, Taga M, Uematsu N, Gondo Y, Ohtaki M, Kominami R and Niwa O (2002). Persistent induction of somatic reversions of the pink-eyed unstable mutation in F1 mice born to fathers irradiated at the spermatozoa stage. *Radiat Res,* **157,** 661–7.

Spandidos D A, Koumantakis E, Sifakis S and Sourvinos G (1998). Microsatellite mutations in spontaneously aborted embryos. *Fertil Steril,* **70**(5), 892–5.

Tsai A F, Kaufman K A, Walker M A, Karrison T G, Odem R R, Barnes R B, Scott J R, Schreiber J R, Stephenson M D and Ober C (1998). Transmission disequilibrium of maternally-inherited CTLA-4 microsatellite alleles in idiopathic recurrent miscarriage. *Reprod Immunol,* **40**(2), 147–57.

United Nations Scientific Committee on the Effects of Atomic Radiation (UNSCEAR) (1988). Sources, Effects and Risks of Ionizing Radiation. Report to the General Assembly, with Annexes. New York, United Nations.

United Nations Scientific Committee on the Effects of Atomic Radiation (UNSCEAR) (1993). Sources and Effects of Ionizing Radiation. Report to the General Assembly, with Scientific Annexes. New York, United Nations.

United Nations Scientific Committee on the Effects of Atomic Radiation (UNSCEAR) (2000). Sources and Effects of Ionizing Radiation. Report to the General Assembly: Volume 2, Annex F: DNA Repair and Mutagenesis. New York, United Nations.

United Nations Scientific Committee on the Effects of Atomic Radiation (UNSCEAR) (2001). Hereditary Effects of Radiation. Report to the General Assembly with Scientific Annex. New York, United Nations.

Vorobtsova I (2000). Irradiation of male rats increases the chromosomal sensitivity of progeny to mutagenes. *Mutagenesis,* **15**, 33–8.

Wiley L M, Kidder G M and Watson A J (1990). Cell polarity and development of the first epithelium. *Bioessays,* **12**(2), 67–73.

Wiley L M, Raabe O G, Khan R and Straume T (1994a). Radiosensitive target in the early mouse embryo exposed to very low doses of ionizing radiation. *Mutat Res,* **309**(1), 83–92.

Wiley L M, Van Beek M E and Raabe O G (1994b). Embryonic effects transmitted by male mice irradiated with 512 MeV/u ^{56}Fe nuclei. *Radiat Res,* **138**(3), 373–85.

Wiley L M, Baulch J E, Raabe O G and Straume T (1997). Impaired cell proliferation in mice that persists across at least two generations after paternal irradiation. *Radiat Res,* **148**, 145–51.

ACKNOWLEDGEMENTS

We wish to acknowledge the following:

Chapters 2 and 3 Dr Mary Lyon, MRC Mammalian Genetics Unit, Harwell, for most helpful comments.

Chapter 4 The authors of the Nuclear Industry Family Study for presentation of their studies which greatly aided our discussions.

THE APPENDICES

APPENDIX A

GLOSSARY

Absorbed dose — The quantity of energy imparted by ionising radiation to a unit mass of matter such as tissue. Absorbed dose has the units J kg^{-1} and the special name gray (Gy). 1 Gy = 1 joule per kg.

Acetylation — Addition of acetyl groups either chemically or enzymatically.

Actinides — A series of 15 radioactive elements with increasing atomic numbers beginning with actinium (89) and ending with lawrencium (103). Many of them decay by the emission of alpha particles. Some can also decay by spontaneous fission or can be made to undergo fission by bombardment with neutrons and are therefore used as nuclear fuels. Only 4 of the actinides – actinium, thorium, protactinium, and uranium – occur in nature in significant quantity; the remaining 11 are produced artificially by bombardment of other related elements with high energy particles.

Aetiology — The study of causes of disease.

Age-standardised rates (ASRs) — For the purposes of this report, for ages 0–14 and 15–24 years, age-standardised rates (ASRs) have been calculated as simple averages of the age-specific incidence rates for the five year age groups they contain. This is equivalent to standardising to a uniform population (with equal numbers in each five-year age group).

ALL — *See leukaemia.*

Allele — In humans the majority of genes come as a pair, one from each parent. Each of the individual copies of the two genes is called an allele and they are not necessarily identical.

Alpha emitter — A radionuclide which decays through emission of alpha particles.

Alpha particle — A charged particle emitted during the radioactive decay of many heavy radionuclides. It is identical to the nucleus of a helium atom, consisting of two protons and two neutrons. An alpha particle has low penetrating power but high linear energy transfer (LET).

AML — *See leukaemia.*

Anaemia — A general term that covers any condition in which the following factors are less than the recognised normal range:

(i) number of red cells in a given volume of blood,

(ii) the amount of the oxygen carrying protein, haemoglobin,

(iii) the volume of red cells in circulation.

Someone becomes anaemic if they do not have enough red cells, or they are not able to produce the haemoglobin to go within those cells. In either situation the amount of protein carrying oxygen around in the blood is low, and as a consequence the individual becomes pale and can develop shortness of breath, lethargy and fatigue, and eventually the anaemia can put a big strain on the heart.

Associations

A relationship between a disease and an exposure. This may be because the exposure causes the disease, or due to non-causal factors.

Ataxia-telangiectasia

A rare and complex genetic disorder in which the patient's cells show an increased frequency of chromosomal abnormalities. The disorder is characterised by progressive degeneration of part of the brain responsible for balance and co-ordination, immunological defects, cells being very sensitive to radiation and a high risk of leukaemia and lymphoma.

Autosomal recessive

A form of inheritance for certain clinical conditions which require both of the two alleles for a single gene to be faulty, eg autosomal recessive conditions such as cystic fibrosis. Individuals with a single faulty copy are unaffected or less affected carriers.

Becquerel (Bq)

The international (SI) unit for the number of nuclear disintegrations occurring per unit time, in a quantity of radioactive material. 1 Bq = 1 nuclear disintegration per second. It replaced the curie (Ci), where 1 Bq = 2.7×10^{-11} Ci. As it is an extremely small unit, levels of activity in Bq are often prefixed with mega (10^6 Bq – MBq), giga (10^9 Bq – GBq) and tera (10^{12} Bq – TBq), particularly in the context of discharges into the environment. Conversely, under normal circumstances, activity concentrations in environmental materials are generally low and so prefixes such as milli (10^{-3} Bq – mBq) and micro (10^{-6} Bq – μBq) may be employed.

Beta emitter

A radionuclide which decays through emission of beta particles.

Beta particle

A particle emitted from a nucleus during the radioactive decay of certain types of radionuclides. It has a mass and charge similar to that of an electron. It has greater penetrative power than an alpha particle, but is low linear energy transfer (LET) radiation.

Bias

In the most general sense, bias is any effect which causes an investigation to give results which differ systematically from the true values, ie errors which are not random errors.

In epidemiology, 'bias' may arise in the particular circumstances where a subset of individuals selected for study are not representative of the population being studied or where the information available for those at different degrees of risk is not comparable. For example, in a cohort study, the exposed group might be more (or less) likely to be lost to follow-up than the unexposed group. In a case–control study, the controls might be more likely than the cases to have forgotten that they were exposed to the agent in question.

Bias is a very serious flaw in epidemiological studies and increasing the study population will not, of itself, reduce the errors (as would be the case if errors were random). Other things being equal, bias is more likely to be a problem in case–control than in cohort studies. In a cohort study, some kinds of bias can be eliminated by studying the whole population at risk rather than a sample, if this is practicable.

Bloom's syndrome A rare and complex genetic disorder in which the patient's cells show an increased frequency of chromosomal abnormalities. The disorder is characterised by retarded growth, immunological defects; cells being sensitive to radiation in some individuals and a high risk of leukaemia, lymphoma and a variety of common cancers.

Bystander effect Genetic damage appearing in unirradiated cells close to irradiated cells.

Case–control study A study in which the risk factors of people with a disease are compared to those without a disease.

Chromosomes Genes are packaged in groups called chromosomes which are visible under the microscope. Different organisms have different numbers of chromosomes and the arrangement and stability of chromosomes is important to the health of the organism. Disturbance in chromosome structure or number may lead to genetic disease (Down's syndrome is an example) or to cancer.

CLL *See leukaemia.*

Cohort study This is a method used in analytical epidemiology. A cohort study is designed to answer the question: 'What are the effects of a particular exposure?' Cohort studies compare a group with the exposure under consideration to a group without the exposure, or with a different level of exposure, or to the country as a whole. The groups (cohorts) are followed over a period of time, and the disease occurrence is compared between the groups or between the cohort and rates expected from national statistics.

Confidence interval Indicates the (im)precision of the study result as a measure of the real size of any risk. In this way a confidence interval conveys the effects of sampling variation on the precision of, for example, age-standardised rates calculated from a limited time period, etc. Specifically, the true rate will be inside the 95% confidence interval on 95% of occasions, although the study rate remains the best estimate of the true value.

Confounding Confounding is a problem in epidemiological studies which arises when there is an exposure which is associated with both the factor that is being investigated and the disease under study. This would give rise to an apparent relationship between the factor being investigated and the disease, even if the factor did not cause the disease. For example, suppose lung cancer was being studied in workers involved to a particular chemical. If those exposed to higher levels of the chemical smoked more than other workers, then the chemical would be associated with lung cancer even if it did not actually cause the disease. The problem can be addressed in the design and analysis of studies but requires that data on the confounder be collected.

Congenital Present at birth.

Daughter product *See decay product.*

Decay The process of spontaneous transformation of a radionuclide. The decrease in the activity of a radioactive substance.

Decay product A nuclide or radionuclide produced by decay. A decay product may be formed directly from a radionuclide or as a result of a series of successive decays through several radionuclides.

DNA A chemical made up of a linear sequence of different molecules called bases (adenine, thymine, cytosine and guanine) constituting the genetic material of organisms. There are four bases and the permuted sequence of these is read as a code which determines the composition and properties of the organism. The simplest organisms such as bacteria have nearly five million bases in their genetic material; humans have more than three-hundred million bases.

DNA methylation The attachment of a methyl group (a $-CH_3$ group) to a cytosine (*see DNA*). This is done routinely, as a way to protect DNA from the enzymes and chemicals produced to destroy foreign DNA, and as a way to regulate transcription of genes in the DNA.

Dose A measure of the amount of radiation received. More strictly it is related to the energy absorbed per unit mass of tissue. Doses can be estimated for individual organs or for the body as a whole. 'Dosimetry' is the science of estimating doses.

Doubling dose The dose at which the mutation frequency is increased to twice the naturally occurring mutation frequency.

Down's syndrome (Trisomy 21) A genetic disorder in which individuals have physical and mental retardation to varying degrees and characteristic facial abnormalities. The cause is nearly always an extra chromosome 21.

Dysmorphic features A body characteristic that is abnormally formed. A malformed ear, for example, is a dysmorphic feature.

Effective dose Effective dose is the sum of the weighted equivalent doses in all the tissues and organs of the body. It takes account of the biological effectiveness of different types of radiation and variation in the susceptibility of different organs and tissues to radiation damage. Thus it provides a common basis for comparing exposures from different sources. Unit sievert (Sv).

Epidemiology Epidemiology is the study of the distribution and putative causes of diseases in human populations. Descriptive epidemiology analyses the age, sex and whereabouts of those who have particular diseases and the methods allow changes in case rates with time or place to be studied and case clusters to be investigated. Analytical epidemiology, on the other hand, investigates possible causes of particular diseases using case–control or cohort approaches.

Epigenetic A heritable change in the properties of a cell that is not due to a mutation in DNA. It usually reflects an alteration in the degree of expression of a gene. Epigenetic changes are not permanent and may be unstable.

Equivalent dose The quantity obtained by multiplying the absorbed dose by a factor to allow for the different effectiveness of the various ionising radiations in causing harm to tisue. Unit sievert, symbol Sv. Usually the factor for gamma rays, X-rays and beta particles is 1 but for alpha particles it is 20.

Exogenous Caused by something originating from outside a cell or animal and not from within.

Expected numbers The number of deaths or cases that would occur to a specified group of people over a given time period if overall mortality or incidence rates in a reference population (usually national) are applied.

External and internal exposures

External exposure arises from radioactive sources which remain outside the body. Internal exposure arises from radioactive materials which are taken inside the body, through inhalation or ingestion. An alpha particle has a very short range and hence very little penetrative power, so that if it were to come from an external source it would be unlikely to penetrate the surface of the skin, giving up most of its energy in the dead surface skin layers. If, however, an alpha particle were emitted from a source that had been inhaled into the lungs its closer proximity to living cells could result in damage to those cells. Internal exposures are generally received from sources that have been inhaled or ingested. Beta and gamma radiation sources can give rise to either internal of external exposures.

Fanconi's anaemia

A rare and complex genetic disorder in which the patient's cells show an increased frequency of chromosomal abnormalities. The disorder is characterised by a complex variety of developmental defects, progressive bone marrow failure and a very high risk of acute myeloid leukaemia.

Fission

The spontaneous or induced disintegration of a heavy atomic nucleus into two or more lighter fragments (nuclei). The energy released in the process is referred to as nuclear energy.

Fragile X-linked mental retardation

Fragile X syndrome is characterised by mental retardation, autistic-like behaviour and other physical abnormalities. Both males and females can be affected, although it is more common in men.

Fusion sequences

Where part of a chromosome has become joined to another chromosome (a type of mutation termed a translocation), a fusion gene composed of parts of genes from the two different chromosomes may be created. For example, the Philadelphia chromosome is the result of a reciprocal translocation between chromosomes 9 and 22 and is present in some people with chronic myeloid leukaemia. Part of the *abl* gene on chromosome 9 is transferred to chromosome 22 (the Philadelphia chromosome) and part of the *bcr* gene from chromosome 22 is translocated to chromosome 9. The Philadelphia chromosome, as it is then known, contains a new fusion gene composed of part of the *bcr* and the *abl* gene.

Gamma rays

High energy photons, without mass or charge, emitted from the nucleus of a radionuclide following radioactive decay, as an electromagnetic wave. They are very penetrating but have a low linear energy transfer (LET).

Gastrochisis

Gastroschisis is an abnormality (defect or hole) in the abdominal wall that allows the abdominal contents to protrude outside the body.

Gene

A unit of genetic material consisting of a specific DNA sequence which usually contains the instructions to produce one type of protein. A gene may exist in more than one form (or allele) thus contributing to the differences between individuals.

Genetic material

The genetic material of almost all organisms is DNA, a chemical comprising a linear sequence of bases constituting a code which determines the properties of the organism.

Genome

The entire genetic material (DNA) of a cell.

Genomic instability

This term applies to a variety of conditions where cells exhibit an increased frequency of chromosomal abnormalities and gene mutations. Many tumour cells are more unstable than normal cells.

Germ cell These are the cells which in the human are present in the ovary or testicles and which divide to become the egg or sperm. In this division only one-half of all the chromosomes are included in the final cell so that when the egg and sperm come together there will be a full chromosome content.

Germ line Usually used to refer to those cells called germ cells as well as the final egg and sperm.

Gonad Organ (testis or ovary) in which germ cells reside.

Gray (Gy) The international (SI) unit of absorbed dose. 1 Gy is equivalent to 1 joule of energy absorbed per kilogram of matter such as body tissue.

Haematopoietic Sometimes spelt hemopoietic, this is a general term which covers all aspects of the process of the formation and development of the various types of blood cells and other formed elements such as platelets, within the blood. It describes the essential process which occurs in the bone marrow for producing all the cellular and particulate components of blood.

Half-life ($t_{½}$) The time taken for the activity of a radionuclide to lose half its value by decay. During each subsequent half-life its activity is halved again so its activity decays exponentially.

Hepatocytes Dividing liver cells.

Histones Proteins found in the nuclei of all cells where they are complexed to DNA.

Hodgkin's disease A form of malignant lymphoma that is characterised by painless enlargement of lymphatic tissue and the spleen and often involves symptoms such as fever, wasting weight loss, anaemia, and night sweats.

Huntington's disease Huntington's disease is a genetic disease with onset between 30 to 50 years of age and characterised by involuntary movements, behaviour changes and dementia. The defect is on the short arm of chromosome 4 and is an autosomal dominant inherited condition.

Hypothesis A suggested explanation for an observed phenomenon, ideally one that can be tested experimentally. *See also null hypothesis.*

ICRP International Commission on Radiological Protection. It consists of experts in radiology, genetics, physics, medicine and radiological protection from a number of countries. Established in 1928, it meets regularly to consider the results of research on the effects of radiation and publishes recommendations on all aspects of radiological protection, including dose limits for man.

ICD (International Classification of Diseases) The World Health Organization periodically publishes International Classifications of Diseases to allow researchers in different countries to classify causes of death and other ill-health in a consistent way. These ICD codes are widely used in epidemiology and in medical statistics.

Incidence The number of instances of illness commencing, or of persons falling ill, during a given period in a specified population. More generally, the number of new events, eg new cases of disease in a defined population, within a specified period of time. The term incidence is sometimes used to denote 'incidence rate'.

Infectious aetiology The process by which disease is brought about by a transmissible agent, eg a virus.

Interuterine	Inside the uterus.
Intraperitoneal	Into the cavity surrounding the intestines, bladder, ovaries, etc.
In utero	A term meaning 'within the uterus (womb)'.
In vitro	*In vitro* means, literally, 'in glass'; a biological or biochemical process occurring outside a living organism.
In vivo	*In vivo* means, literally, 'in life'; a biological or biochemical process occurring within a living organism.
Ion	Electrically charged atom or grouping of atoms.
Ionisation	The process by which a neutral atom or molecule acquires or loses an electron. The production of ions.
Ionising radiation	Radiation which is sufficiently energetic to remove electrons from atoms in its path. In human or animal exposures, ionising radiation can result in the formation of highly reactive particles in the body which can cause damage to individual components of living cells and tissues.
Isotope	Nuclides containing the same number of protons (ie same atomic number) but different number of neutrons.
Karyocyte	General scientific term for any cell with a nucleus.
Leukaemia	A group of malignant diseases of the blood-forming tissues in which normal control of cell production breaks down and the cells that are produced are abnormal. Leukaemia (L) can be classified as either lymphoid (L) or myeloid (M) and as either acute (A) or chronic (C) (eg ALL, AML, CLL and CML). Lymphoid and myeloid refer to the type of white cell affected. If this is a lymphocytic cell the condition is called lymphocytic or lymphoblastic leukaemia. Myeloid leukaemias affect any of the other types of white blood cells or the red cell or platelet-producing cells. Acute leukaemias develop quickly and progress rapidly; chronic leukaemias are slower to develop and slower to progress.
Leukaemogenic	Possessing the ability to cause leukaemia.
Li-Fraumeni syndrome	An inherited family trait carrying an increased risk of cancer during childhood and early adulthood.
Linear energy transfer (LET)	A measure of the density of ionisation along the track of an ionising particle in biological tissue or other medium. Particles or rays of radiation are generally described as having a high or low LET, ie their tracks leave high or low density deposits of energy.
LNHL	Abbreviation that stands for leukaemia and non-Hodgkin's lymphoma.
Locus (plural: loci)	A particular site on a chromosome, usually used to refer to the gene present at that site.
Lymph nodes	Bean-shaped masses of tissue situated along the course of the lymphatic vessels which help protect against infection. A source of lymphocytes.
Lymphocyte	A type of white blood cell that is part of the body's immune system.

Lymphoma (L) A malignant tumour of the lymphatic system (lymph nodes, reticulo-endothelial system and lymphocytes).

Malignancy Cancerous growth, a mass of cells showing uncontrolled growth, a tendency to invade and damage surrounding tissues and an ability to seed daughter growths to sites remote from the primary growth.

Methylation pattern *See DNA methylation.*

Microdeletions Deletion of a small piece of chromosome or DNA sequence.

Microsatellites A short sequence (less than ten bases) of repeated DNA in a genome. Some are related to certain genetic diseases such as fragile X-linked mental retardation and Huntington's disease.

Minisatellites Regions of DNA dispersed throughout the genome consisting of repetitive sequences of ten or more bases. In some ('hypervariable minisatellites') the number of repeated DNA bases are unstable and different in almost every individual – a property utilised in 'DNA fingerprinting'.

Monoclonal origin A group of cells (eg in a tumour) that originated in a single cell.

Multiclonality A group of cells (eg in a tumour) that arose from more than one cell.

Multiple significance testing *See statistical significance.*

Mutagen An agent that increases the mutation rate.

Mutation A permanent alteration in the genetic material of a cell that is transmitted to the cell's offspring. Mutation may be spontaneous (the result of accidents in the replication of genetic material) or induced by external factors (eg ionising radiation and certain chemicals).

Mutation rate The frequency of mutation per unit time (usually expressed as per cell generation).

Myotonic dystrophy A common myotonic disorder which affects many systems of the body in addition to muscle. While the disease has manifested itself by the age of 25 years in most cases, some affected individuals or family members may escape developing significant symptoms throughout their lives.

Neurofibromatosis type 1 Also known as von Recklinghausen's disease, is present in about 1 : 3000 live births. It is characterised by the presence of pale brown spots on the skin and the formation of numerous benign soft tumours arising from the abnormal growth of nerves. The spots may be present at birth or infancy, and the tumours appear in late childhood or early adulthood; the latter can sometimes result in grossly disfiguring effects owing to their large size. The course of the disease is progressive in most cases.

NHL *See non-Hodgkin's lymphoma.*

Non-Hodgkin's lymphoma (NHL) A group of lymphomas which differ in important ways from Hodgkin's disease and are classified according to the microscopic appearance of the cancer cells. In children, NHL and leukaemias are often combined due to historical difficulties in making diagnostic distinctions.

Nuclear site, establishment or plant	A facility which includes a nuclear reactor and/or capability for handling radionuclides associated with the nuclear fuel cycle.
Nuclear reactor	A structure in which neutron-induced nuclear fission can be sustained and controlled in a self-supporting chain reaction. In power reactors, the heat produced by fission is absorbed by coolant, producing steam which in turn powers a turbine for generating electricity. Some reactors can be put to other uses, eg materials testing and plutonium production. In a thermal reactor the fission is brought about by slow or thermal neutrons which are produced by slowing fast neutrons by the use of a moderator such as carbon or water. In a fast reactor, most of the fission is produced by fast neutrons and therefore requires no moderator. Most thermal reactors use uranium as fuel, in which the uranium-235 content has been artificially raised (this fuel is known as enriched uranium). Fast reactors use a mixture of plutonium and uranium dioxide.
Nuclear reprocessing	The processing of spent fuel from a nuclear reactor, to remove fission products and to recover fissile and fertile material for further use. Chemical solvents play a major role in this process.
Null hypothesis	The statistical hypothesis that one variable has no association with another variable or set of variables, or that two or more population distributions do not differ from one another.
Odds ratio	The ratio of the odds of disease occurrence in a group with exposure to a factor to that in an unexposed group; within each group, the odds are the ratio of the numbers of diseased and non-diseased individuals. This is the measure of association used in case–control studies and provides a close approximation of the relative risk.
Oncogene	An oncogene is a gene that has been changed (mutated) from its original form, the proto-oncogene, such that it initiates cancer.
One- and two-sided tests	When there is an *a priori* reason to be interested in increases rather than decreases in risk, then researchers may choose to use 'one-sided tests', ie a test in one direction only, and a 90% confidence interval. However, if equal weight is to be given to both increases and decreases in risk, then a 'two-sided test' (ie a test in both directions) and a 95% confidence interval may be used. In both instances a result will be said to have reached the conventional ($p < 0.05$) level of statistical significance if the probability is 1 in 20 or less that a result at least as extreme as that observed arose in the absence of an underlying effect. In the case of a one-sided test attention is focused on the upper 5% of the distribution and no attention is paid to results in the lower tail. In the case of a two-sided test, a result would be described as significant if it fell above the upper 2.5 percentile or below the lower 2.5 percentile of the distribution. Thus a result which was described as significant if a one-sided test was applied might not achieve significance under a two-sided test. *(See also p-value.)*
p-value	A p-value provides an idea of the strength of the evidence against the null hypothesis. A low p-value points to rejection of the null hypothesis. The commonly used significant value is 0.05. On this basis, any result giving a p-value less than 0.05 would be regarded as significant and lead to rejection of the null hypothesis in favour of an alternative hypothesis.
Parental preconceptional irradiation (PPI)	Irradiation of either the father or the mother before conception of a child. It has been hypothesised (see below) that this irradiation of male or female germ cells might lead to a risk of cancer or to some other harm in the offspring, rather than in the irradiated individuals.

Parental preconceptional irradiation hypothesis — A hypothesis suggesting that radiation-induced mutations in the germ line cause a predisposition to leukaemia or NHL in the next generation.

Phagocytic — A cell that is capable of taking up particulate material by invagination of its outer membrane.

Phenotype — The physical characteristics of a cell or organism as determined by the genes.

Phosphorylation — The process of adding a phosphate to a molecule. Phosphates consist of phosphorus and oxygen. Phosphate molecules are an important component of nucleic acids such as DNA.

Plutonium (Pu) — Radioactive chemical element of the actinide series in Group IIIb of the periodic table, atomic number 94. It is the most important transuranium element because of its use both as fuel for certain types of nuclear reactors and in nuclear weapons.

Point mutation — A change (mutation) in a single gene. The smallest change is the deletion or insertion of a single base or the substitution of a single base by another.

Power — The power of a study is its potential ability to reject the null hypothesis in favour of a specified alternative hypothesis. In mathematical terms, power is specified as the probability that the null hypothesis can be rejected, based on a test with specified statistical significance.

For example, the null hypothesis might be that a specific agent carries no increased risk of a particular disease; the alternative hypothesis, that it doubles risk. A planned study may then be estimated to have, say, a 90% probability of rejecting the null hypothesis of no increased risk, based on a test at the 5% level, if the alternative hypothesis were true.

In radiation epidemiology, the power of a study will, other things being equal, increase with

(i) the number of study subjects and the period of observation,

(ii) the difference in radiation dose between the exposed group and those with whom comparisons are being made,

(iii) the size of the radiation-induced effect,

(iv) the rarity of the endpoint considered in the comparison group.

Power calculations are normally made while a study is being planned. Once a study has been analysed, confidence intervals on possible risks allow deductions about their true magnitude to be made.

PPI — *See parental preconceptional irradiation.*

Population mixing — The population mixing hypothesis proposes that childhood leukaemia can be a rare response to a common but unidentified infection (hence the absence of marked space–time clustering). Epidemics of this (mainly sub-clinical) infection are promoted by influxes of people into rural areas, where susceptible individuals are more prevalent than the average. Such influxes would increase population density and hence the level of contacts between susceptible and infected individuals, thereby increasing the risk of childhood leukaemia.

Preconceptional effect — An event, like mutation, that occurs in the germ cell before conception (fertilisation), ie while still in the gonad.

Progeny Offspring of person, animal or plant.

Protein kinases Any of several enzymes that phosphorylate amino acid residues in specific proteins.

Proto-oncogenes Genes that may mutate into oncogenes.

Radionuclide A type of atomic nucleus which is unstable and which may undergo spontaneous decay to another atom by emission of ionising radiation (usually alpha, beta or gamma).

Radioactive discharges Some establishments produce radioactive waste as byproducts and this is disposed of, usually to the environment, as radioactive discharge.

Radioactivity The property of radionuclides of spontaneously emitting ionising radiation. Measured in becquerels (Bq).

Relative risk (RR) A ratio of the risk of disease or death of those exposed to the risk to those not exposed to the risk.

Repeat sequences *See minisatellites, microsatellites and tandem repeats.*

Reprocessing *See nuclear reprocessing.*

Reticulo-endothelial system A term originally introduced to describe all the phagocytic cells of the body. It has been superseded by the more specific term mononuclear phagocyte system reflecting their cellular origins and relationships.

Risk The probability that an event will occur, eg that an individual will become ill or die within a stated period of time or age. Also, a non-technical term encompassing a variety of measures of the probability of a (generally) unfavourable outcome. *(See also relative risk.)*

RR *See relative risk.*

Sievert (Sv) The international (SI) unit of effective dose, obtained by weighting the equivalent dose in each tissue in the body with ICRP-recommended tissue weighting factors, and summing over all tissues. Because the sievert is a large unit, effective dose is commonly expressed in millisieverts (mSv) – ie one-thousandth of one sievert, and microsieverts (μSv) – ie one-thousandth of one millisievert. The average annual radiation dose received by members of the public in the UK is 2.6 mSv.

Significance test A result that lies outside the range of values expected to occur, if some specified hypothesis is true, is said to be statistically significant. A probability (p-value) of 0.05 for such an occurrence is commonly used to separate 'significant' from 'non-significant' results. This boundary is arbitrary.

Somatic cell A cell of the body other than germ line cells such as sperm or egg.

Specific locus tester system Specially bred mouse strains that allow the detection of heritable mutations in offspring of exposed parents, principally by looking at changes in coat colour.

Spinocerebellar ataxia A rare neurological disease of the central nervous system which manifests itself as uncoordinated movement. The onset is slow.

Standardised incidence ratio (SIR) As standardised mortality ratio, but referring to the incidence of disease rather than death.

Standardised mortality ratio (SMR)

The ratio of the number of deaths in the study group or population to the expected number. The expected number is calculated assuming that the age- and sex-specific death rates applying to the population under study are those taken as the 'reference rates'. These will often be those of the national population but may also be taken from a smaller area (eg the south west of England or Cumbria).

Statistical significance and multiple significance testing

In an investigation of, for example, whether exposure to a particular agent is associated with a certain type of cancer, statistical tests will be carried out to assess the probability that a result at least as extreme as that observed could have arisen by chance if the null hypothesis were true. Researchers will commonly describe a result as statistically significant if this probability is 5% (1 in 20) or less. *(See also p-value.)*

If associations between the agent and two distinct types of cancer are tested, then, even in the absence of any underlying effect, the chance that one of these tests will achieve statistical significance as defined above would be about 10%. If three or more tests are carried out, the probability that one of the p values is 5% or less becomes even greater. Unless there is a special reason (a 'prior hypothesis') to suggest that one particular type of cancer may be associated with exposure to the agent, it is difficult to interpret the individual p-values. The usual assumption, that a p-value of less than 5% is unlikely to reflect a chance association, is inappropriate because the multiple significance testing means that an apparently significant result has an increased probability of arising.

Stem cell

A cell that has the capacity to produce identical daughter stem cells or cells that develop into the mature specialised cells for a particular tissue such as blood or muscle.

Sub-telomeric chromosomal region

A region near the ends of chromosomes rich in repeated sequences of DNA bases.

Tandem repeats

Multiple copies of the same base sequence on a chromosome.

Telomere-like array

See sub-telomeric chromosomal region.

Topoisomerase II

An enzyme that changes the degree with which the DNA is supercoiled by cutting both strands of DNA.

Transgenerational effect

In this report, an effect in the offspring resulting from exposure of a parent to some risk factor.

Tritiated water

Water that contains tritium. Tritium is a radioactive isotope of hydrogen having the symbol T or ^{3}H, with two neutrons and one proton in the nucleus and thus an atomic mass of 3; formed by bombarding lithium with low energy neutrons, it has a half-life of 12.33 years.

Tumour

Mass of tissue formed by unregulated growth of cells; can be either benign or malignant.

Two-sided test

See one- and two-sided tests.

Uranium (U)

A hard grey metal which exists in seven isotopic forms (uranium-233 – uranium-239) of which the two most important are uranium-235 (the only naturally occurring readily fissile isotope) and uranium-238. Both isotopes decay through a series of decay products which emit alpha, beta and gamma radiation. Principal source of fuel for nuclear reactors.

Urethane	Chemical used in the plastics industry. The main components of scooter, skate and skateboard wheels.
Virus	A biological entity that can reproduce only within a host cell. Viruses consist of nucleic acid *(see DNA)* covered by protein. Once inside the cell, the virus uses the capability of the host cell to produce more viruses.
X-irradiation	X-ray radiation. Photons with energy greater than about 100 electron volts (eV) usually emitted by an X-ray machine or an excited atom.

APPENDIX B

COMMITTEE ON MEDICAL ASPECTS OF RADIATION IN THE ENVIRONMENT

CHAIRMAN

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Professor M D Mason MD FRCP FRCR
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Dr G J Draper OBE MA DPhil FFPH
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Dr R Hamlet BSc PhD CBiol MIBiol (Scientific)

Dr Jill Meara MA MSc BMBCh FFPH (Medical)

Dr G Kendall BSc MSc PhD (Scientific)

Miss Jane Bradley MRSC CChem

Dr Nezahat Hunter BSc PhD

Miss Julie Kedward (Administrative)

The Secretariat wish to thank Mrs Alison Jones (NRPB) for her work on the glossary and reference sections of this report.

ASSESSORS IN ATTENDANCE REPRESENTING THE FOLLOWING ORGANISATIONS

Department for the Environment, Food and Rural Affairs

Department of Health

Department of Health, Social Services and Public Safety (Northern Ireland)

Department of Trade and Industry

Health and Safety Executive

Scottish Environment Protection Agency

Environment Agency

Information and Statistics Division, Common Services Agency, NHS in Scotland

Medical Research Council

Food Standards Agency

Ministry of Defence

National Assembly for Wales

National Radiological Protection Board

Office for National Statistics

Scottish Executive

TRANSGENERATIONAL EFFECTS SUBCOMMITTEE

Chairman

Professor B A Bridges

Members

Professor R A Cartwright
Dr G Draper
Professor K K Cheng *(until March 2000)*
Professor J Little
Professor T J McMillan
Professor Louise Parker
Professor A M R Taylor
Professor J Thacker
Professor J M A Whitehouse *(until March 2002)*
Professor E Wright

Secretariat

Dr C Sharp *(until March 1999)*
Mrs Julia Thomas *(until April 1999)*
Dr R Hamlet
Dr M Little *(from April 1999 to March 2000)*
Dr G Kendall *(from February 2000)*
Dr Nezahat Hunter *(from March 2000)*

Assessors

Dr Hilary C Walker
Department of Health

Mr M K Williams *(until March 2000)*
Ms Karen Davies *(from March 2000 to March 2002)*
Ms Wendy Bines *(from April 2002)*
Health and Safety Executive

Dr M Quinn
Office for National Statistics

APPENDIX C

DECLARATION OF MEMBERS' INTERESTS CODE OF PRACTICE

Introduction

1 This code of practice guides members of COMARE as to the circumstances in which they should declare an interest in the course of the Committee's work.

2 To avoid any public concern that commercial interests of members might affect their advice to Government, Ministers have decided that information on significant and relevant interests of members of its advisory committees should be on the public record. The advice of the Committee frequently relates to matters which are connected with the nuclear industry generally and, less frequently, to commercial interests involving radioactivity and it is therefore desirable that members should comply with the Code of Practice which is set out below.

Scope and definitions

3 This code applies to members of COMARE and sub-groups or working groups of COMARE which may be formed.

4 For the purposes of this Code of Practice, the 'radiation industry' means:

(a) companies, partnerships or individuals who are involved with the manufacture, sale or supply of products processes or services which are the subject of the Committee's business. This will include nuclear power generation, the nuclear fuel reprocessing industry and associated isotope producing industries, both military and civil;

(b) trade associations representing companies involved with such products;

(c) companies, partnerships or individuals who are directly concerned with research or development in related areas;

(d) interest groups or environmental organisations with a known interest in radiation matters.

It is recognised that an interest in a particular company or group may, because of the course of the Committee's work, become relevant when the member had no prior expectation this would be the case. In such cases, the member should declare that interest to the Chairman of the meeting and thereafter to the Secretariat.

5 In this code, 'the Department' means the Department of Health, and 'the Secretariat' means the secretariat of COMARE.

Different types of interest – definitions

6 The following is intended as a guide to the kinds of interests which should be declared. Where a member is uncertain as to whether an interest should be declared he or she should seek guidance from the Secretariat or, where it may concern a particular subject which is to be considered at a meeting, from the Chairman at that meeting. Neither members nor the Department are under an obligation to search out links between one company

and another, for example where a company with which a member is connected has a relevant interest of which the member is not aware and could not reasonably be expected to be aware.

If members have interests not specified in these notes but which they believe could be regarded as influencing their advice they should declare them to the Secretariat in writing and to the Chairman at the time the issue arises at a meeting.

Personal interests

6.1 A personal interest involves payment to the member personally. The main examples are:

(a) Consultancies or employment: any consultancy, directorship, position in or work for the radiation industries which attracts regular or occasional payments in cash or kind.

(b) Fee-paid work: any work commissioned by those industries for which the member is paid in cash or kind.

(c) Shareholdings: any shareholding in or other beneficial interest in shares of those industries. This does not include shareholdings through unit trusts or similar arrangements where the member has no influence on financial management.

Non-personal interests

6.2 A non-personal interest involves payment which benefits a department for which a member is responsible, but is not received by the member personally. The main examples are:

(a) Fellowships: the holding of a fellowship endowed by the radiation industry.

(b) Support by industry: any payment, other support or sponsorship by the radiation industry which does not convey any pecuniary or material benefit to a member personally but which does benefit their position or department, eg:

(i) a grant from a company for the running of a unit or department for which a member is responsible;

(ii) a grant or fellowship or other payment to sponsor a post or a member of staff in the unit for which a member is responsible. This does not include financial assistance for students, but does include work carried out by postgraduate students and non-scientific staff, including administrative and general support staff.

(iii) the commissioning of research or work by, or advice from, staff who work in a unit for which the member is responsible.

(c) Support by charities and charitable consortia: any payment, other support or sponsorship from these sources towards which the radiation industry has made a **specific and readily identifiable** contribution. This does not include unqualified support from the radiation industry towards the generality of the charitable resource.

Trusteeships: where a member is trustee of a fund with investments in the radiation industry, the member may wish to consult the Secretariat about the form of declaration which would be appropriate.

Members are under no obligation to seek out knowledge of work done for or on behalf of the radiation industry within departments for which they are responsible if they would not reasonably expect to be informed.

Declaration of interests

Declaration of interests to the department

7 Members should inform the Department in writing when they are appointed of their current personal and non-personal interests and annually in response to a Secretariat request. Only the name of the company (or other body) and the nature of the interest is required; the amount of any salary, fees, share-holding, grant, etc, need not be disclosed to the Department. An interest is current if the member has a continuing financial involvement with the industry, eg if he or she holds shares in a radiation company, has a consultancy contract, or if the member or the department for which he or she is responsible is in the process of carrying out work for the radiation industry. Members are asked to inform the Department at the time of any change in their personal interests, and will be invited to complete a form of declaration once a year. It would be sufficient if changes in non-personal interests are reported at the next annual declaration following the change. (Non-personal interests involving less than £1000 from a particular company in the previous year need not be declared to the Department.)

Declaration of interests at meetings and participation by members

8 Members are required to declare relevant interests at Committee meetings and to state whether they are personal or non personal interests. The declaration should include an indication of the nature of the interest.

(a) If a member has a current (personal or non-personal) interest in the business under discussion, he or she will not automatically be debarred from contributing to the discussion subject to the Chairman's discretion. The Chairman will consider the nature of the business under discussion and of the interest declared (including whether it is personal or non-personal) in deciding whether it would be appropriate for the relevant member to participate in the item.

(b) If a member has an interest which is not current in the business under discussion, this need not be declared unless not to do so might be seen as concealing a relevant interest. The intention should always be that the Chairman and other members of the Committee are fully aware of relevant circumstances.

9 A member who is in any doubt as to whether he or she has an interest which should be declared, or whether to take part in the proceedings, should ask the Chairman for guidance. The Chairman has the power to determine whether or not a member with an interest shall take part in the proceedings.

10 If a member is aware that a matter under consideration is or may become a competitor of a product process or service in which the member has a current personal interest, he or she should declare the interest in the company marketing the rival product. The member should seek the Chairman's guidance on whether to take part in the proceedings.

11 If the Chairman should declare a current interest of any kind, he or she should stand down from the chair for that item and the meeting should be conducted by the Deputy Chairman or other nominee if he or she is not there.

12 Some members of the Committee may, at the time of adoption of this note, or (in the case of new members) of their joining the Committee, be bound by the terms of a contract which requires them to keep the fact of the contractual arrangement confidential. As a transitional measure, any member so affected should seek to agree an entry for the public record (see paragraph 14) with the other party. If such agreement does not prove possible, the members shall seek a waiver permitting them to disclose their interest, in confidence, to the Chairman and the Secretariat. The Secretariat will maintain a confidential register of such disclosures which will not form part of the public record.

13 On adoption of this note members shall not enter into new contractual obligations which would inhibit their ability to declare a relevant interest.

Record of interests

14 A record will be kept in the Department of the names of members who have declared interests to the Department on appointment, as the interest first arises or through an annual declaration, and the nature of the interest.

15 Information from the record will be made available by the Secretariat to bona-fide enquirers and published by any other means as and where the Department deems appropriate.

Members' declarations of interests – 2003

Member	Company	Personal interest	Company	Non-personal interest
Prof F Alexander		None		None
Dr T Atkinson		None	UKAEA	Consultancy
Dr H R Baillie-Johnson		None		None
Prof B Bridges		None		None
Prof R Cartwright		None		None
Prof O Eden		None		None
Dr C J Gibson		None		None
Prof A Elliott		None	1 Nycomed Amersham 2 CIL Ltd	1 PhD students 2 Equipment loan for collaborative project
Prof N Haites		None		None
Prof J Little		None		None
Prof T McMillan		None	Westlakes Research Inst	PhD students and consumables
Prof M D Mason		None		None
Prof L Parker		None		None
Dr R A Shields	Amersham plc British Energy	Small shareholdings		None
Dr M Spittle		None		None
Prof A M R Taylor		None		None
Prof J Thacker		None		None
Prof R Waters		None		None
Prof E Wright		None		None