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

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.

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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. The Black Advisory Group had been commissioned in 1983, by the then Minister of Health, to investigate reports of a high incidence of leukaemia occurring in young people living in the village of Seascale, which is directly adjacent to the Sellafield nuclear site. This Group also investigated the suggestion that there might be an association between the level of leukaemia incidence and the radioactive discharges from Sellafield. In its Report (Black 1984), the Advisory Group confirmed that there was a higher incidence of leukaemia in young people resident in the area. The Advisory Group also concluded that the estimated radiation dose from the Sellafield discharges and other sources, received by the local population, could not account for the observed leukaemia incidence on the basis of knowledge available at that time. The uncertainties in the available data led the Advisory Group to make recommendations for further research and investigation.

iii. The first recommendation made by the Black Advisory Group was that a case–control study should be carried out using the records of those cases of leukaemia and lymphoma which had been diagnosed among young people up to the age of 25 years, resident in West Cumbria. This study was carried out by the MRC Epidemiology Unit in Southampton and published in 1990 (Gardner et al, 1990). The authors of this study, which became known as the 'Gardner Report', 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.

iv. As part of our Fourth Report (COMARE, 1996) we undertook a review of all the data published both before and after the Gardner Report which was relevant to the hypothesis that paternal preconceptional irradiation is associated with the risk of childhood leukaemia in subsequent offspring. Although we concluded in 1996 that other studies had not confirmed the hypothesis put forward by Gardner and his colleagues, we were aware that further studies designed to investigate this hypothesis were still under way. These studies included two of the largest epidemiological studies ever undertaken in the UK. We said, therefore, that we would return to this topic when all of these studies were completed.

v. In this our Seventh Report we have examined the results of all of the studies commissioned by the Co-ordinating Committee on Health Aspects of

Radiation Research (CCHARR). These included four laboratory studies and two epidemiological studies. We also considered other relevant biological and epidemiological studies. 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. To aid in assessing all the complex scientific data we set up the Transgenerational Effects Subcommittee (TES). The membership of this Subcommittee and COMARE are given in Appendix B of this report.

vi. In the preparation of this report, COMARE 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.

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

CHAPTER 1

INTRODUCTION

1.1 The Black Advisory Group was commissioned in 1983, by the Minister of Health, to investigate reports of a high incidence of leukaemia in young people living in the village of Seascale, adjacent to the Sellafield nuclear site and the suggestion that there might be an association between the leukaemia incidence and the radioactive discharges from Sellafield. In its Report (Black, 1984), the Advisory Group confirmed that there was a higher incidence of leukaemia in young people resident in the area. It also concluded that the estimated radiation dose from the Sellafield discharges and other sources, received by the local population, could not account for the observed leukaemia incidence, on the basis of knowledge available at that time. The uncertainties in the available data led the Advisory Group to make recommendations for further research and investigation. In 1984 the Advisory Group recommended a series of studies on individuals who had lived near Sellafield. These included a recommendation for a case–control study to investigate relevant features of cases of leukaemia and lymphoma in the area.

1.2 The Department of Health (DH) and the Medical Research Council (MRC) subsequently funded a study, undertaken by the late Professor Martin Gardner and his colleagues in Southampton, to investigate factors that could be relevant to the development of leukaemia and lymphoma in young children (Gardner et al, 1990). While this study was under way we, the Committee on Medical Aspects of Radiation in the Environment (COMARE), noted in our Second Report (COMARE, 1988) that many of the people who live near Sellafield and Dounreay were workers at the nearby installations. This raised the possibility that the excess of childhood leukaemia could be related to parental occupation at these nuclear installations. There was no direct evidence for this but two mechanisms were identified by which such an effect could theoretically be mediated. One of these previously unrecognised pathways of radiation exposure was that workers could inadvertently, bring radioactive material home. The second was the possibility of an effect on the germ cells (sperm, egg and their precursor cells) of the parents of cases, prior to conception.

1.3 In our Second Report we pointed out that some animal experiments suggested that preconceptional parental exposure could (in certain circumstances) lead to malignancy in offspring by inducing a particular sort of heritable change. At that time there was no evidence of this from the limited data available in humans, but we drew attention to the possibility that parents occupationally exposed to radiation might be at above average risk of having children with leukaemia and that this needed to be explored. In both our Second and Third Reports (COMARE, 1988, 1989), the Committee recommended that studies should be set up to consider any possible effects on the health of the offspring of parents occupationally exposed to radiation. The DH and the Health and Safety Executive (HSE) were in the process of doing this when the Gardner team published its findings.

Gardner case–control study

1.4 From the results of this study Professor Gardner and his colleagues concluded that:

'The raised incidence of leukaemia, particularly, and non-Hodgkin's lymphoma (NHL) among children near Sellafield was associated with paternal employment and recorded external dose of whole body penetrating radiation during work at the plant before conception. The association can explain statistically the observed geographical excess. This result suggests an effect of ionising radiation on fathers that may be leukaemogenic in their offspring, though other, less likely, explanations are possible.'

This result was dominated by four case fathers with exposure of more than 100 mSv total preconceptional dose or estimated to be more than 10 mSv during the six months before conception. A dose–response effect was also seen, in that the highest risk was associated with the highest accumulated radiation doses before conception.

The authors speculated that:

'Since radiation badge recordings will reflect gonadal dose we interpret this finding to suggest an effect of the radiation exposure on germ cells producing a mutation in sperm that may be leukaemogenic in subsequent offspring.'

However, the authors also pointed out that:

'Other explanations may be possible, such as exposure to internally incorporated radionuclides or other concomitant exposures in the workplace: it has not been possible to examine the first of these so far, and the second seems unlikely...Additionally contamination of the home with radioactive or other material through occupational exposure may be relevant ....'

The so-called 'Gardner hypothesis' has never been formally defined. For the purposes of this report we intend to interpret this hypothesis as follows:

That exposure to radiation alone, at the levels experienced by male workers in the British nuclear industry by whatever route, is linked to the incidence of leukaemia and NHL in their offspring conceived after they were irradiated and that this incidence is dose dependent.

Health and Safety Executive study

1.5 The Health and Safety Executive **(**HSE), in a subsequent case–control study (HSE, 1993, 1994), found a statistical association between the incidence of childhood leukaemia and NHL and the fathers' total external preconceptional radiation dose. This study was largely based on the same cases used in the Gardner et al study. However, it used better dosimetric data than was available to Professor Gardner's team. The controls in this study were children born in West Cumbria between 1950 and 1990 who had not been diagnosed with cancer before the age of 25 years and whose fathers had worked at Sellafield. The association, however, was confined to the population of Sellafield workers who started work at the plant before 1965 and who were resident in Seascale at the time of their child's birth.

1.6 The HSE study showed that, for fathers resident outside Seascale when their child was born, there was no association between preconceptional radiation dose and the incidence of childhood leukaemia and NHL. Also, while an association was reported for children born in Seascale between the incidence of these diseases and the father's external radiation dose in the 12-week period before conception, this was not statistically significant. No association was found for cancers other than leukaemia and NHL taken together nor for any other factors studied such as internal radiation dose, chemical exposures or involvement in contamination incidents.

COMARE Interim Statement on the Gardner study

1.7 As noted earlier, in both our Second and Third Reports, we had recommended that studies should be set up to consider any possible effects on the health of the offspring of parents occupationally exposed to radiation. Government was considering how to address these recommendations when Gardner et al published their study. At that time these two disease conditions (leukaemia and non-Hodgkin's lymphoma) tended to be regarded as closely related or as part of the spectrum of a single disease and we have used the abbreviation LNHL to describe those conditions. It should be noted that the current view is that leukaemia and NHL have distinct clinical characteristic that may also relate to their aetiology.

1.8 The interim COMARE statement (COMARE, 1990), made following the publication of the Gardner study, reaffirmed the need for further major epidemiological studies. We recommended that these studies should be given high priority and that a study involving direct approaches to workers to obtain information on the health of their children and also a study linking records of childhood cancer and leukaemia would be complementary and that both should be undertaken (COMARE, 1990).

1.9 COMARE also made further recommendations for biological research to address the Gardner hypothesis and stated that both of the epidemiological studies already recommended should be designed to test this hypothesis. In view of the considerable interest in the issue, COMARE also recommended that there needed to be some form of co-ordination of research, to ensure the best possible use of resources and to avoid duplication of effort.

Co-ordinating Committee on Health Aspects of Radiation Research

1.10 In 1990, DH and HSE jointly established the Co-ordinating Committee on Health Aspects of Radiation Research (CCHARR) to manage Government-sponsored research to investigate the association suggested by Professor Gardner and his colleagues. CCHARR was used to formalise invitations to tender not only for epidemiological studies but also for laboratory studies which might demonstrate biological mechanisms having a bearing on Gardner's epidemiological results. Subsequently, four laboratory-based studies and two epidemiological studies were commissioned.

1.11 The first of these two epidemiological studies, known as the Record Linkage Study (RLS), and another epidemiological study concerning UK medical radiographers and their children were the subject of a COMARE interim statement on the health of children born to radiation workers (COMARE, 1998). One of the laboratory studies could not be completed for technical reasons, but the remaining CCHARR studies have now been completed and published.

Conclusions of the COMARE Fourth Report relating to the Gardner hypothesis

1.12 The suggestion that parental preconceptional exposure to a mutagen may lead to an increased risk of cancer in the offspring was first made in an epidemiological study of the effects observed following exposure to diagnostic X-rays (Graham et al, 1966). This hypothesis, which we will refer here to as the parental preconceptional irradiation (PPI) hypothesis and which includes exposure of mothers as well as fathers, unlike the Gardner hypothesis, has been the subject of numerous experimental and epidemiological studies since that time. If it were true it would imply that radiation-induced mutations occur in the germ line and cause a predisposition to cancer in the next generation. In our Fourth Report (COMARE, 1996) we considered, in depth, whether PPI could be a contributory factor in the incidence of childhood leukaemia found in the village of Seascale near to the Sellafield site. During the preparation of that Report we reviewed the possible effects of preconceptional irradiation on subsequent childhood cancers. To do that we asked the Department of Health to organise two seminars dealing with the biological mechanisms of such effects and the epidemiological evidence supporting

any such findings. To these seminars were invited as many as possible of the scientific experts in this and related fields. The opinions expressed were considered and included in Chapter 4 of our Fourth Report.

1.13 In summary, we noted that the majority of LNHL occurs sporadically. Around one to five percent of LNHL occurs in association with other conditions such as Down's syndrome, Ataxia-telangiectasia, Fanconi's anaemia, Bloom's syndrome, Li-Fraumeni (and L-F like) syndrome, Neurofibromatosis Type 1 and some types of genetic immunodeficiency. In some of the above conditions, radiation used in treatment may increase the risk of subsequent leukaemia.

1.14 We concluded that whilst the PPI hypothesis can be sustained in principle, the implied level of risk of LNHL at Seascale, when compared to known radiation-induced mutation rates for other specific genetic effects, was inconsistent with the accepted dosimetry. It had been suggested that the measured dose of external radiation might be a surrogate measure for internal exposure to radionuclides or to chemicals. However, the HSE study found no association between internal dose to fathers and the risk of leukaemia in their offspring. Furthermore, there is no evidence implicating any exposure to radionuclides or chemicals that has been unique to those Sellafield workers resident in Seascale. Quantitative considerations led us to conclude that the size of those PPI effects expected on theoretical grounds or demonstrated in animals were too small by at least an order of magnitude to explain the Seascale childhood leukaemia excess.

1.15 At the time of publication of our Fourth Report, we held the view that there is no *a priori* reason why a mutation conferring predisposition to leukaemia/lymphoma should not be induced and transmitted to the offspring of a radiation-exposed person. We stated that the questions that needed to be addressed were:

(i) whether or not the radiation doses to which radiation workers were exposed would have been sufficient to induce mutations at a frequency that would be necessary to account for the incidence of leukaemia/lymphoma in their children, and

(ii) whether or not the predisposition conferred by any such mutation would be strong enough to result in the disease in a sufficiently high proportion of cases.

1.16 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 carcinogenic effects in the children of radiation workers in the United Kingdom. We have reviewed in depth the genetic, biological and epidemiological data that has become available since the time of publication of our Fourth Report. Descriptions of this new work are contained in Chapters 2, 3, 4 and 5 of this our Seventh Report. Our deliberations and conclusions concerning this topic are the subject of Chapter 6 and summarised in Chapter 7 and our recommendations are contained in Chapter 8.

CHAPTER 2

THE SEASCALE CLUSTER OF CANCER CASES IN YOUNG PEOPLE

2.1 As a result of investigative journalism in 1983, Seascale village (see the map on page 12) and other areas in West Cumbria were identified as the sites of alleged clusters of cases of childhood cancer. The Advisory Group set up to investigate this assertion (Black, 1984) took the view that the investigation of the cases from the village should be set in the context of rates for wider areas of Cumbria and the UK as a whole. The Advisory Group did not take a view as to which cancers might be in excess nor in exactly which age group, preferring to use the term 'young people'. The parental preconceptional irradiation (PPI) hypothesis was proposed by Professor Gardner on the basis of the results of his study of childhood cancer in West Cumbria. We, therefore, take this opportunity of reviewing the current status of the Seascale cluster.

2.2 Exhaustive studies in rates of cancer were undertaken by the Advisory Group which stated that the age group of interest was under 25 years at diagnosis and that the excess of interest was in 'lymphoid cancer', ie only acute lymphoblastic leukaemia (ALL), based on four Seascale cases in 0–4 year olds diagnosed from 1968–1982. The Advisory Group concluded that other areas of Cumbria had little sign of case excesses and then concentrated analyses on Seascale. The analyses ignored four earlier cases from 1954–1967 (acute myeloid leukaemia (AML), non-Hodgkin's lymphoma (NHL), ALL and neuroblastoma), did not consider an additional early osteosarcoma as relevant, and did not formally incorporate two cases diagnosed in 1983 and 1984 (both NHL).

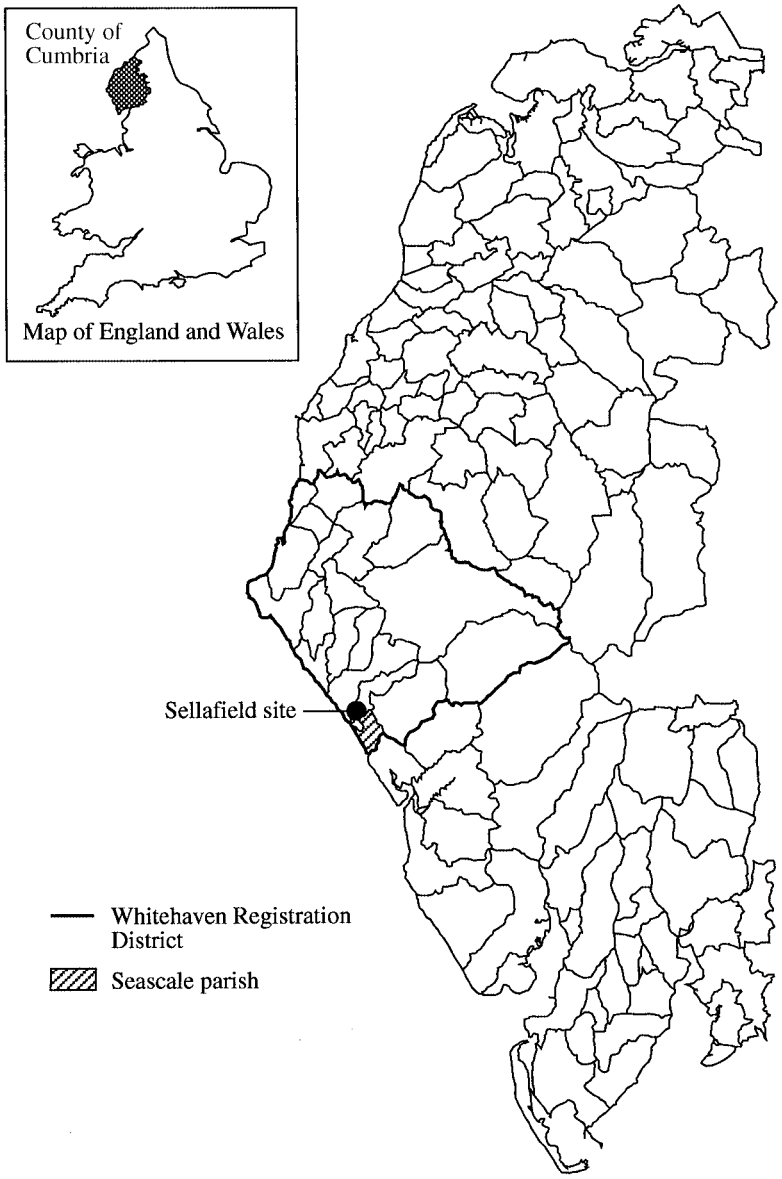
2.3 An updated analysis (Draper et al, 1993) incorporated further cases but only formally analysed cases diagnosed from 1968–1988, ie not the early cases nor the case of ALL diagnosed in 1991. This analysis combined ALL and NHL as 'lymphoid cancer'. The constraints on the time span of the analyses gave the impression that ALL, with four cases, was the dominant cancer of the cluster (1968–1979).

2.4 No epidemiological analysis of all the possible cases has ever taken place. However, the Draper et al study concluded that there is roughly a ten-fold excess for both the leukaemias and solid tumours.

2.5 The magnitude of risk, prolonged time scale, the age range and the diversity of different cancers make this case excess unique.

2.6 There are, however, some complexities relating to the study of the Seascale cases. It is not straightforward to decide upon the exact composition of the cancer cases occurring in the village. The early studies have emerged with different case lists (Black 1984; Draper et al, 1993; COMARE, 1996) and during the time period of the existence of COMARE, new cases have been diagnosed.

2.7 For the purpose of putting the various studies into context, it seems appropriate to list all of the cases known to COMARE and then explain why some might or might not be thought of as part of the true case cluster.



Seascale village and surrounding area: the map shows the boundaries of civil parishes within Whitehaven Registration District, Cumbria

Source: **UKBORDERS™, University of Edinburgh – this map is based on data provided with the support of the ESRC and JISC and uses boundary material which is copyright of the Crown and the ED-LINE Consortium.**

2.8 Table 2.1 gives a list of all known cases of malignant neoplasms diagnosed at ages 0–24 known to COMARE and who were born or diagnosed or who died in Seascale from 1954 to 1991. Extensive searches have been made, prior to 1954, but no further cases can be identified from 1906 to 1953. Since 1991 and up to 2001 three further cases have been found, two in children under 15 living in the village (a ganglioneuroblastoma and a central nervous system (CNS) tumour) and one NHL in a young adult aged under 25 years who lived most of her life in the village but was diagnosed elsewhere. These cases are incorporated into Table 2.2. Tables 2.1 and 2.2 are probably complete as regards mortality for the period 1906–2001 and, because of the very low survival rates before 1950 and the extensive studies of the village made since then, may well include all cases diagnosed in this period. Most cases born in the village from 1950 onwards and diagnosed by 2001 will have been identified by the various research studies undertaken in this period.

Table 2.1 Malignant neoplasms among people age 0–24 years who were born or diagnosed or who died in Seascale, 1906–1991*

Case	Year of diagnosis	Age at diagnosis	Diagnosis‡	Notes
A	1954†	12†	Osteosarcoma	Died in Seascale Diagnosed elsewhere
B	1954	6	Neuroblastoma	
C	1954	3	Subacute lymphatic leukaemia	
D	1955	7	ALL	
E	1955	2	NHL	
F	1957	4	Wilms' tumour	
G	1960	2	AML	
H	1968	11	ALL	
I	1968	4	ALL	
J	1971	2	ALL	
K	1975†	15†	Rhabdomyosarcoma	
L	1978	20	CML	
M	1979	5	ALL	
N	1983	9	NHL	
O	1984	1	NHL	
P	1985	18	Pinealoma (CNS tumour)	
Q	1988	23	NHL	
R	1988	17	HD	
S	1991	16	ALL	

* This table includes only malignant neoplasms; we have not included the case of essential thrombocythemia reported by Cartwright et al (2001) (their case 17).
† Year and age at death, age at diagnosis not known.
‡ See text for abbreviation.

Table 2.2 Malignant neoplasms at ages 0–24 who were born or diagnosed or who died in Seascale: this table includes all cases known to have been diagnosed or to have died between 1954 and 2001

	0–14 years		15–24 years		
	Male	**Female**	**Male**	**Female**	**TOTAL**
ALL	2	4	1	0	**7**
AML	1	0	0	0	**1**
CML	0	0	1	0	**1**
HD	0	0	0	1	**1**
NHL*	1	2	0	2	**5**
CNS*	0	1	1	0	**2**
Neuroblastoma*	2	0	0	0	**2**
Wilms' tumour	0	1	0	0	**1**
Rhabdomyosarcoma	0	0	0	1	**1**
TOTAL	**6**	**8**	**3**	**4**	**21*,†**

* Includes the three most recent cases.
† Case A excluded.

2.9 Three of the cases could be omitted from any analyses. Case A has no claim to be part of the cluster, because although he died in the village, he was diagnosed elsewhere in the northwest of England and subsequently moved to Seascale. Cases C, L and the recent NHL were all born in the village, but were diagnosed elsewhere in the UK. Case F died outside Seascale – place of diagnosis unknown.

2.10 If case 'A' is omitted but the other cases included then Table 2.2 gives the composition of the cluster to date. There are seven cases aged over 14 years at diagnosis and overall an almost equal number of males and females. The two commonest conditions are ALL (seven cases) and NHL (five cases). There are more cases of LNHL than solid tumours, but there are more non-leukaemia cases than the leukaemias.

2.11 It is difficult to define the incidence of all the cancer cases due to the lack of detailed knowledge of the village population. It is known, for example, that rapid change in population size took place from 1950–1960 and that the turnover of the population year on year was large. This means there are very large uncertainties in the estimated rates of childhood cancer. When, however, the relative frequency of the diagnoses are compared to the diagnostic grouping in England and Wales of cancers in those aged 0–14 and 15–24 years, the main proportionate excess lies in the NHL diagnoses followed by ALL.

2.12 Little is known of the cause of most cancers in either children or young adults. It is possible ALL in certain subtypes is related to aspects of genetic susceptibility and responses to infection (Greaves and Alexander, 1993) whilst sub-types of NHL are linked to profound immune suppression (Kinlen, 1992), eg HIV infection or the immune suppression post renal transplantation. Hodgkin's disease (HD) in the children is linked to Epstein Barr Virus infection (Jarrett et al, 1996) whilst the causes of AML, CML and rhabdomyosarcoma, neuroblastoma and Wilms' tumour are generally unknown. CNS tumours may have a genetic predisposition (Tijssen et al, 1982). In view of the varied embryological cells of origin of these cancers and the pathological processes which create these conditions, it is quite possible the causes of all these conditions are diverse.

2.13 It is generally accepted that there are a number of criteria that need to be met before a factor can be taken to be causally associated with disease. The three most relevant here are:

(i) the endpoint (childhood cancer) should be shown to be quantitatively related to the postulated causal factor,

(ii) the amount of the causal factor needs to be sufficient to account for the observed excess of cases,

(iii) there should be a plausible biological mechanism by which the factor gives rise to the endpoint.

For clarity, we have formulated these criteria as if a single cause was responsible for the entire excess. It is, of course, possible that two or more factors act at the same time.

2.14 The most obvious candidate factor was exposure of children to radioactivity released from Sellafield, since radiation is a known cause of leukaemia and many other cancers and the relation with dose is known fairly well. However, successive reports have ruled this out since there has not been sufficient exposure to radiation to account for the number of cases of childhood cancer and there is no general increase in adult cancer in the area such as

might occur if a substantial unrecognised source of environmental radioactivity had existed.

2.15 Two hypotheses have been proposed to account specifically for the leukaemia cases. These are discussed in detail in Chapter 6, but a brief outline is given here. One hypothesis, proposed by Professor Leo Kinlen, is that the excess childhood leukaemias are a consequence of extensive migration into a remote rural area (Kinlen, 1995; see also 'population mixing' in the glossary). This hypothesis supposes that some infectious agent is involved in the development of at least some leukaemias. In our Fourth Report we did not consider that the quantitative relation between population mixing and childhood leukaemia was well enough established for us to be able to account for the excess cases in and around Seascale. Since then there have been advances in this area and it now looks as though population mixing could account for around half of the cases of leukaemia, although this estimate has limits of uncertainty which could encompass all the cases or, at the other extreme, one or perhaps none of them (see Chapter 5). Nevertheless, while an infectious agent is thought by many experts to be involved in childhood leukaemia, it has not yet been identified and the biological mechanism for the population mixing hypothesis remains speculative.

2.16 The other hypothesis was proposed by Professor Martin Gardner who found that there was an association between the number of cases and the total radiation dose received at work by their fathers. He suggested that the initiating changes occurred in the father's germ cells, ie those that gave rise to the sperm which conceived the affected child. The problem with this hypothesis is that there is no known radiation-induced germ cell change that is known to cause leukaemia or other cancers, and also occurs with sufficient frequency at the doses received by the fathers to account for the observed number of cases. Moreover, the association reported by Gardner and his colleagues has not been found in studies carried out on radiation workers anywhere else.

2.17 Thus, neither of these hypotheses on their own, currently meets the criteria needed to establish the causes of the cluster of childhood leukaemia around Sellafield. It is, of course, possible that the above criteria may eventually be met by one or both of these hypotheses. Even so, only part of the problem would be resolved since childhood leukaemias comprise less than half the excess cases in Seascale. Moreover, no single hypothesis necessarily covers all the cancer diagnoses in the cluster.

CHAPTER 3

RADIATION-INDUCED MUTATION IN THE GERM LINE AND SOMATIC CELLS OF MAMMALS

3.1 It is noted in Chapter 1 that the Gardner hypothesis implies a level of risk inconsistent with historic data on radiation-induced mutagenesis. These data are reviewed briefly below, together with recent experimental evidence for novel mechanisms of radiation-induced mutation. The new data indicate that relatively high frequencies of radiation-induced mutation occur in some parts of the mammalian genome, and that radiation has persistent effects that may lead to adverse responses in organisms at long times after irradiation. Thus, parental preconceptional irradiation (PPI) can potentially give rise to mutations in offspring through at least two mechanisms: firstly, by direct alteration of specific genes in the germ line, and secondly by radiation-induced effects in germ cells that may cause alteration in genes not directly hit, or that may persist in subsequent generations and so increase the overall probability of mutation.

3.2 Mutations are inherited changes in the sequence of the genetic material (DNA). They may be measured using genetic tests in animals, and in both animals and cultured cells mutations may also be determined by looking directly at the DNA. Most studies have measured mutations in known DNA sequences, genes or chromosomes shortly following irradiation, often for ease of investigation. Mutations in some of these genes have known consequences in man; for example, genes involved in cancer (proto-oncogenes) may be used to obtain data relevant to cancer formation. Similarly, larger mutations such as chromosomal rearrangements can be caused by radiation, and specific rearrangements are also known to be involved in certain forms of cancer, including leukaemias.

3.3 Despite extensive efforts, attempts to detect radiation-induced mutations in the offspring of survivors of the atomic bombs dropped on Hiroshima and Nagasaki or in the offspring of cancer patients given radiotherapy have been inconclusive. The most comprehensive data on the mutagenic effects of ionising radiations on mammalian germ cells have, therefore, come from studies with laboratory mice. The majority of these data were derived from genetic systems in which the mutation frequency was measured at several specific sites in the genome (loci) following irradiation of the germ cells of adult mice. To detect mutations at single loci, which may contain one or more functional genes, relatively high radiation doses were used. Irradiation of large numbers of mice, and breeding these to reveal the mutations, has allowed accurate estimates of radiation-induced frequencies of mutation at several loci (UNSCEAR, 1993). The use of such genetic systems has provided an extensive database on radiation mutagenesis that has been subject to periodic review and commentary. The general conclusions of these studies are as follows:

(i) Mutational sensitivity varies among loci, mainly because some of the induced mutations will lead to inviability and such mutations will go undetected. The fraction of mutations which is inviable varies among loci.

(ii) Sensitivity to mutation induction varies at different stages of germ cell development.

(iii) Many radiation-induced mutations are lethal when both gene copies are affected.

3.4 The use of mammalian somatic cells for radiation mutagenesis studies of specific genes has given support to the mouse studies, particularly in understanding the molecular nature of the induced mutations (Thacker, 1992; UNSCEAR, 2000). Thus, while radiation can induce all types of mutations, from very small* to very large changes in the genetic material (DNA), both the somatic and germ line studies show that large losses (deletions) and rearrangements of DNA commonly occur following irradiation. The proportion of radiation-induced mutations that have such large changes is often more than fifty per cent, but varies from gene to gene. It is likely that the amount of genetic damage associated with many radiation-induced mutations will commonly lead to cell death. This has led to the suggestion that only a small proportion of the genes that are associated with disease in humans can sustain such mutations without incurring cell death (Sankaranarayanan and Chakraborty, 2000). That is, most human disease-associated mutations are likely to be small genetic changes (such as single DNA base substitutions), because these are capable of generating subtle changes of function in protein products that are compatible with development of the whole organism. Also, some dominantly expressing disorders are dependent upon subtle protein changes. Thus it is thought that the increase in incidence of genetic diseases produced by a given dose of radiation is likely to be proportionally less than the overall increase in gene mutation frequency.

3.5 Recently mutations have also been measured at unconventional loci and at long times following irradiation, potentially revealing novel mechanisms of radiation-induced genetic change. Frequencies of mutation in the somatic cells of mice, as measured by the *pink-eyed unstable* locus, are linear with X-ray dose down to 10 mGy and occur at least 100 times more frequently per unit dose than germ line mutations in the mouse specific-locus tests (Schiestl et al, 1994). It should be noted that mutation of *pink-eyed unstable* is unlike the mutations measured in the specific-locus tests, being caused by loss of a duplicated part of the *pink eyed* locus. There are also a number of recent reports of very high frequencies of radiation-induced mutation in certain repeat sequences in the germ cells of mice. Several groups have reported that changes in the sequence of unstable tandem-repeat sequences (minisatellites) can be seen in the offspring of male mice exposed to radiation, and that these changes occur at a frequency far greater than can be accounted for by conventional mutation rates or the number of radiation damage sites in the DNA (Dubrova et al, 1998; Fan et al, 1995; Sadamoto et al, 1994). However, there is disagreement in the literature on which germ cell stage (spermatogonia or spermatids) is most prone to mutation induction, and additional methodological work is required to reconcile such discrepancies. In one recent study the progeny of male mice exposed to fission neutron irradiation and mated to unexposed mice were found to have a 6-fold increase in minisatellite mutation frequency; remarkably, the mutation frequency remained high in male (6-fold) and female (3.5-fold) progeny of the next generation, derived from further breeding to unexposed females (Dubrova et al, 2000). Some of the mutations in minisatellites occurred early in development, leading to clustering of mutations in the germ cell population, but even when these clusters were ignored the

* These mutations are often termed ‘point’ mutations, and commonly alter one or a few base pairs in a gene; in some studies the sizes of point mutations have not been documented precisely, but are considered to be no larger than the affected gene.

mutation frequency in second-generation male progeny remained significantly elevated. Both Dubrova et al (2000) and Niwa and Kominami (2001) have reported that elevated mutation frequencies can also be found in the unirradiated female allele in F1 progeny. It has to be concluded that a mechanism exists in male germ cells of mice that can extend the consequences of radiation damage to DNA sequences that have not been damaged directly.

3.6 Minisatellite changes have also been reported in children whose parents were subjected to fallout from Chernobyl although both parents and children would have been exposed to other pollutants (Dubrova et al, 1996, 1997). No increase in minisatellite mutation frequency was found in the children of the Japanese atomic bomb survivors (Kodaira et al, 1995; Satoh and Kodaira, 1996) or in those of Chernobyl clean-up workers (Livshits et al, 2001) and a recent paper reports on the failure to detect any increase in minisatellite mutations in three subjects given radiotherapy for seminoma (May et al, 2000). In contrast, a recent paper (on the offspring of Chernobyl clean-up workers (Weinberg et al, 2001) reports changes in bands observed with RAPD, a method that looks for changes in random DNA sequences (not specifically repeat sequences). There were fewer DNA sequence alterations where more time elapsed between exposure and conception. Unfortunately, the nature and site of the changes were not determined, and insufficient technical information was given to enable the significance the work to be properly evaluated. Nevertheless, a similar suggestion that the time between irradiation and conception might be important was found in the work of Livshits et al (2001). A small but non-significant increase was found for those children born while their fathers were working at the Chernobyl site or up to two months later compared to those born more than four months after their fathers had stopped working at the site. Such a decrease implies that the mutations found had been induced in cells passing through spermatogenesis rather than in stem cells, and might explain the failure to detect increases in mutation frequency in other human studies.

3.7 Minisatellites are not part of the genetic coding sequence but there is evidence that they may affect the expression of adjacent genes. This has been shown to occur with minisatellites associated with the insulin and *H-ras* genes and certain of these minisatellite alleles are associated with a modest increase in risk of insulin-dependent diabetes and several cancers including non-Hodgkin's lymphoma (Bennett et al, 1995; Calvo et al, 1998; Gosse-Brun et al, 1999; Kennedy et al, 1995; Krontiris et al, 1993; Lindstedt et al, 1999; Phelan et al, 1996). Recently, a minisatellite expansion has been associated with a form of progressive epilepsy (Lafreniere et al, 1997; Virtaneva et al, 1997) and it is now clear that the number of 24 base repeats inserted in the prion protein PRNP gene can alter the probability of conversion to a pathogenic form of the protein and can determine both susceptibility to Creutzfeldt-Jakob disease and the disease phenotype (Chiesa et al, 2001; Cochran et al, 1996; Owen et al, 1992; Rossi et al, 2000; Skworc et al, 1999; Vital et al, 1999). The fact that mutation at certain minisatellites occurs in the male germ line of mice at frequencies greater than found in coding sequences is considered as evidence for a transient genome instability induced by radiation in male germ cells. This instability associated with certain minisatellites is not genome wide and its consequences are uncertain, at present there is no evidence for or against the hypothesis that changes in the sequence of minisatellites affect the incidence of childhood cancer.

3.8 There are many different types of repeat sequences in the mammalian genome in addition to minisatellites; these include very short tandem repeats (microsatellites), and repeats that cap the ends of chromosomes (telomeric repeats). An increase in the number of repeats within a microsatellite ('expansion') has been implicated in several human disorders, such as fragile

X-linked mental retardation, Huntington's disease, myotonic dystrophy, and spinocerebellar ataxia (Cummings and Zoghbi, 2000). At present there is little evidence to support or refute the possibility that radiation can induce an increase in the frequency of changes in these repeat sequences. However, an increase in alterations has recently been reported at a microsatellite locus in the offspring of mice exposed to quite low doses (10–50 cGy) of chronic irradiation (Vasil'eva et al, 2001). It has also been found that such increases are induced in experimental organisms by breakage of DNA, a form of damage readily caused by radiation (Richard and Paques, 2000).

3.9 Effects on animals and cells may also occur at relatively long times after irradiation, suggesting that persistent genetic instability is induced. Mutation frequency has been found to be elevated in clones of cells for as much as 50–100 cell generations after irradiation, and these mutations were found to be predominantly small genetic changes (Little et al, 1997). The occurrence of chromosome changes has also been found to occur several cell generations after irradiation; for example, cultured bone marrow cells showed persistent chromosomal aberrations following alpha-particle irradiation (Kadhim et al, 1992). The transplantation of irradiated bone marrow cells into mice suggested that this form of instability persisted for periods of up to one year (Watson et al, 1996), although the direct irradiation of mice with either X-rays or alpha particles from radium-224 did not induce excess transmissible chromosome instability in a 100-day period following exposure (Bouffler et al, 2001). There is also evidence from the analysis of chromosomal instability in different mouse strains that there is a link between delayed effects and sensitivity to radiation-induced cancer (Ponnaiya et al, 1997; Yu et al, 2001). Taken with the high mutation frequencies found in some DNA sequences (see above), these experimental data suggest that radiation may cause some 'untargeted' events in cells which may result in genetic changes at certain sites in DNA and at long times following irradiation. These events may have a number of possible causes, including: persistence of the damaging agent (in particular, reactive oxygen species and peroxides), persistence and amplification of sites of DNA damage, misrepair of damage leading to genome rearrangements which themselves upset the correct functioning of the cell (position effects on blocks of genes), and the induction of stable epigenetic changes (eg alteration of DNA methylation patterns). The contribution of these changes to radiation-induced cancer incidence is uncertain at present; where an accumulation of genetic changes is required as part of carcinogenesis these changes may conceivably have a role to play.

3.10 In considering the likely impact of the mechanisms and types of radiation mutations on the incidence of disease-associated mutations in humans, it may be asked whether the data are representative of the responses of the mammalian genome overall. Firstly, since only a handful of genes have been assessed out of a current estimate of approximately 35,000 in the genome (International Human Genome Sequencing Consortium, 2001), it seems premature to state whether these are representative. Some commentators believe that the genes used for the majority of the mouse mutation experiments (the seven specific-loci tester system) may overestimate the average radiation-induced gene mutation frequency, based on comparisons of data from a variety of other experiments with the mouse (Neel and Lewis, 1990). However, much of this additional information relies upon relatively small numbers of mutations scored, so that statistical errors are relatively large. This is perhaps illustrated by the fact that the doubling doses* for acute low-LET radiation for these different sets of data vary between 0.1 and

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

4 Gy. It may be prudent therefore to retain a risk estimate based on the major sources of data: for example, the doubling dose estimate of 0.4 Gy for acute and 1 Gy for chronic low-LET radiation. Secondly, in the recent studies of mini-satellite mutation in the mouse germ line, despite the high mutation frequencies, the doubling dose for acute low-LET radiation is approximately the same as that for the seven specific loci (0.33 Gy). Finally, there is evidence that the mutations arising in somatic cells at long times following radiation exposure (radiation-induced genetic instability) are not large deletions but mainly small mutations (Little et al, 1997). These recent data illustrate the problems in predicting the response of mammalian genomes to radiation, especially with regard to the proportions of different types of mutations induced, in addition to the established fact that the fraction of small mutations detected is dependent on the gene assessed. Uncertainties of extrapolation of the mouse data to man are increased by difficulties of knowing whether human disease-associated genes will respond in the same way as in the mouse.

CHAPTER 4

CANCER IN THE OFFSPRING OF IRRADIATED PARENTS: LABORATORY STUDIES

Background

4.1 At the time of our Fourth Report only limited experimental animal data existed concerning parental preconceptional irradiation (PPI) effects and possible carcinogenic outcomes. Non-carcinogenic transgenerational effects were well known. For example, congenital malformations in offspring following preconceptional irradiation of mice have been clearly demonstrated by Nomura (1975) and confirmed by others (Lyon and Renshaw, 1986; Russell and Kelly, 1982). A body of experimental work had also been built up by Nomura that supports the hypothesis that PPI is associated with the induction of tumours in the offspring (Nomura, 1992). The largest increases occurred in the incidence of lung tumours and their incidence rate was further raised by the exposure of the offspring to a second carcinogen, urethane. There was also a small increase in the rate of leukaemia in the offspring of the exposed mice.

4.2 As noted in Chapter 1, the Co-ordinating Committee on Health Aspects of Radiation Research (CCHARR) commissioned specific biological laboratory studies, all of which are now published. In addition, since we last reviewed the field in our Fourth Report, several other biological studies have been published which are of relevance. In this chapter we describe and discuss the results of these studies and their implications. We have tried to include all appropriate studies after a dedicated literature search and a computer MEDLINE search. It is not possible to cite all the papers to which we have had access but we have noted those which will allow other researchers to undertake their own review; indeed we are aware of a recent review by Lord (1999) (see below) which covers much of this field.

New evidence from experimental and animal models

4.3 Studies by Cattanach et al were specifically designed to replicate the work of Nomura (1982), although different mouse strains were used. Cattanach et al (1995) exposed male mice having a high natural incidence of lung tumours to either 0, 2.5 or 5 Gy X-rays and found no evidence for the influence of paternal irradiation on the occurrence of tumours. For each of three groups of mice about 600 offspring were investigated for the incidence of lung tumours. However, other expected indications of radiation-induced effects were found, such as smaller average litter sizes. A second study (Cattanach et al, 1998) repeated this investigation with a different strain of mice, both with and without exposure to the tumour promoter, urethane. Again no radiation enhanced tumour induction was observed in the offspring. Thus these studies have shown no evidence of a PPI effect on tumour incidence following exposure to radiation alone. The data also demonstrated that the number of lung tumours induced varied over the period of experimentation in different cohorts of animals. Iwasaki et al (1996) demonstrated very similar results to Cattanach et al (1995) in C57BL/6 mice. Male mice were irradiated with 3 Gy of cobalt-60 gamma rays, their offspring being allowed to live out their normal life span. There were no significant differences in the survival curve and mean life span of irradiated or control animals. There were no significant differences in incidence or age distributions of tumours with the exception of a *decrease* in the incidence of histiocytic sarcoma in daughters of irradiated males. The other radiation effect of significant reduction in litter size was observed, although there was no change in sex ratio.

Preconceptional irradiation laboratory studies: discussion in our Fourth Report (1996)

In our Fourth Report (COMARE, 1996) we considered the experimental animal data which were available from the then current investigations into PPI effects and possible carcinogenic outcomes. We noted that non-carcinogenic transgenerational effects were well known. For example, congenital malformations in offspring following preconceptional irradiation had been clearly demonstrated by Nomura (1975) and confirmed by others (Lyon and Renshaw, 1986; Russell and Kelly, 1982). In the work of Lyon, the total malformations in the first generation offspring (F1) was 12% and in the second generation (F2) 2.6%.

A substantial body of experimental work had been built up by Nomura which lent support to the PPI hypothesis (Nomura et al, 1992). Nomura had reported the incidence of leukaemia in the offspring of three strains of irradiated mice. The numbers of leukaemias were small and there was considerable variation between the three strains and between the various germ cell stages. Even so, the calculated mutation rates (0 to 6.9 x 10^{-6} per mSv for irradiation of spermatogonia and 1.9 to 13.8 x 10^{-6} per mSv for spermatozoa) were of an order of magnitude higher than those of recessive specific locus, dominant cataract and enzyme activity mutations in mice which involve known numbers of gene loci. They were, however, close to the apparent rates for major skeletal mutations in mice where the number of loci is unknown. A subsequent study carried out with a different strain of mice by Cattenach et al (1995) had failed to confirm Nomura's finding.

In our report we pointed out that if mutations predisposing to the appearance of a malignant disease in the next (F1) generation could be induced in paternal germ cells it would, on the basis of what is known about radiation-induced mutation rates, be fairly difficult to demonstrate experimentally because of the very large numbers of animals that would be required. We noted that even the rates reported by Nomura were insufficient to account for the apparent dose-related excess of childhood leukaemia in the offspring of Sellafield workers.

4.4 In another study designed to repeat the work of Nomura, Daher et al (1998) used one of the same strains of mouse (N5) that was used in the Nomura studies. N5 mice were exposed to 5 Gy of X-rays or intraperitoneal injections of tritiated water over a 30-day period (estimated exposure of 1.5 Gy). The paternal X-irradiation did not achieve statistically significant ($p = 0.07$) doubling of the leukaemia/lymphoma incidence rate in the offspring. Exposure of the parents to tritiated water resulted in a several-fold increase of leukaemia in offspring, which diminished with time and was no longer significant after a period of 12 months. The leukaemia incidence in the offspring of fathers treated with tritiated water was dependent on the maturation stage of the sperm-forming cells during the period of exposure. Vorobtsova (2000) has also reported that chromosomal sensitivity to radiation is increased in the hepatocytes, bone marrow cells and cultivated fetal fibroblasts from the F1 progeny of male outbred rats irradiated with 4.5 Gy X-rays relative to the progeny of unirradiated controls.

4.5 A study by Mohr et al (1999) was also designed to test the findings of Nomura. There were no statistically significant differences in tumour incidence in the progeny of irradiated fathers compared to the appropriate control groups and this finding is contrary to the PPI hypothesis. Paternal urethane treatment prior to conception also did not result in significantly altered incidence or malignancy of tumours of the lung, liver or haematopoietic tissue in the offspring.

4.6 Lord et al (1998) examined tumour induction by a chemical mutagen following preconceptional paternal contamination of mice with plutonium-239. The study set out to investigate whether PPI could render offspring more vulnerable to secondary exposure to an unrelated carcinogen. The results demonstrated an excess of chemical-induced leukaemia in the offspring of irradiated animals compared to non-irradiated animals. The authors conclude that this effect is a result of PPI and may be related to inherited changes that affect the development of haematopoietic stem cells. This study by Lord et al was set up to test earlier observations by the same group that changes to stem cells after radiation predispose to sensitivity to a secondary insult in the offspring. The results, which are interpreted in terms of tissue damage, are interesting and demonstrate an important interaction between radiation and a chemical mutagen.

4.7 Lord (1999) has recently reviewed the literature relating to the Gardner hypothesis. He covers the epidemiological and experimental studies as well as those relating to population mixing and leukaemia and NHL. He discusses possible mechanisms by which PPI might induce increased susceptibility to leukaemia in the offspring of irradiated individuals. He points out the lack of epidemiological support for the Gardner hypothesis but notes that experimental data suggest that such an effect can be demonstrated, at least in some animal strains.

Results of human studies

4.8 It has been suggested that if radiation exposure of male workers at Sellafield before conception could cause leukaemia in their children this might show up in parallel changes to the white blood cells of the fathers of affected children. A study was commissioned by CCHARR and carried out by Cole and her colleagues at the MRC Cell Mutation Unit in Sussex. The frequency of a particular type of mutation was determined in the white blood cells of 18 workers with a recorded cumulative dose of 500 mSv and compared to a matched control group with a cumulative dose of less than 50 mSv. The results of the study by Cole et al (1995) show no evidence that male radiation workers at Sellafield exhibited higher mutation frequencies in peripheral blood lymphocytes, in fact they tended to have lower mutation frequencies. There was, therefore, no reason to believe that Sellafield workers had been subjected to major unrecorded mutagenic radiation exposures.

4.9 It is possible that a mutation in parental germ cells might result in leukaemia in the offspring. Mathematical modelling by Rinaldi et al (1999) suggested that any such patient would be especially prone to multiple independent leukaemia events leading to multiclonality in terms of cell of origin. To test this hypothesis, in the absence of biological material from the Seascale cases Rinaldi and his co-workers carried out a search for multi-clonal leukaemia in infant and childhood ALL. This study was based on the fact that more than one successive mutation is required in the DNA for a cell to become leukaemogenic. If one of these changes were to take place in the father prior to conception there would be a different pattern of genetic change in the leukaemic blood cells of the child than if all the changes occurred in childhood. These patterns would be detectable with current techniques. Bone marrow samples from children with ALL were examined and in all cases the origin of the leukaemia was found to be in a single cell (ie of monoclonal origin). The authors suggest that these results are consistent with the hypothesis that childhood leukaemia originates from damage to a single cell in that child and not to damage to the genes inherited from its parents prior to conception. A possible difficulty with the interpretation of monoclonality in leukaemia is that it could reflect the selection of one rapidly growing clone at an early time in the development of the disease. However, COMARE accepted the conclusion that

these findings suggest that both infant and childhood ALL is of a single-cell origin and implies that leukaemic predisposition resulting from a mutation in a germ cell is unlikely to have a major role in their pathogenesis.

Discussion and conclusions

4.10 COMARE considers the results of the studies of PPI effects in mice show a marked strain effect. For example, the Cattanach studies did not show the same results as the earlier Nomura studies that had used different mouse strains. Similar discrepancies were seen between the results presented by Mohr and Daher. Whilst the rate of induced leukaemia in the Nomura studies is too low to account for the Gardner findings, it is itself too high to be explained by the conventional induction rate for gene mutations. The mechanism by which the Nomura effect is mediated is under study in mice but remains obscure. We know that radiation-induced changes can occur in certain DNA sequences in both germ line and somatic cells at a rate far greater than conventional mutations and studies with cultured mammalian cells have revealed that radiation can elicit genomic instability (see Chapter 2). It has also been observed that unirradiated cells in culture can show genetic damage if they are in close proximity to irradiated cells (the so-called bystander effect, see Grosovsky 1999). Such a phenomenon might explain the findings of Nomura but there is no direct evidence to support this possibility.

4.11 Even if the PPI effect observed in mice by Nomura and other workers were applicable to humans, the magnitude of the effect would still be insufficient to account for an association between the raised incidence of childhood leukaemia and lymphoma in the area around Sellafield with occupational radiation exposure of fathers. This point has been equally strongly made by Professor Nomura himself (Nomura, 1993, and personal communication), and is borne out by the findings of the limited number of human studies so far carried out.

CHAPTER 5

EPIDEMIOLOGICAL STUDIES OF CHILDHOOD CANCER AND PARENTAL RADIATION EXPOSURE

Introduction

5.1 Since the publication of the paper by Gardner et al (1990), a number of studies have examined the hypothesis of a link between occupational paternal preconceptional radiation and childhood cancer. These studies have similarly examined the possibility of a link with prior radiation exposure of the mother. However, the smaller number of female workers with significant radiation exposures generally reduces the power of the latter investigations.

5.2 A number of these studies are discussed in this chapter, three from the United Kingdom, one from North America and one from Germany. These are: the Record Linkage Study (RLS), the Nuclear Industry Family Study (NIFS), the Extended Cumbrian Study, the US 'Three Site Study' and a German study. We also outline some other studies which are of relevance. The investigators presented results in terms of relative risks, odds ratios, hazard ratios and rate ratios. For present purposes, these may be regarded as the same, and the term relative risk will be used throughout.

Record Linkage Study

5.3 The RLS was a case–control study in which the parents of children who developed cancer and of matched control children were identified. Record linkage techniques were then used to determine which of these parents were included on the National Registry for Radiation Workers (NRRW). The NRRW is a register including details of most classified radiation workers in the United Kingdom and also certain other non-classified workers. Details of the study are given in Draper et al (1997a,b).

5.4 Cases of childhood cancer were identified from both the National Registry of Childhood Tumours and the Oxford Survey of Childhood Cancers. In addition, cases and controls from the study conducted in Scotland and North-west England by Kinlen et al (1993) were included. This Scottish study is thus subsumed within the RLS. The dataset contained information on 35,949 children aged between 0 and 14 years old who were born between 1952 and 1986 and diagnosed with cancer before the end of 1986 together with matched controls. Kinlen's original study included only children with leukaemia and non-Hodgkin's lymphoma born and diagnosed up to the end of 1990, and all these cases and their controls including those born and/or diagnosed between 1987 and 1990 were incorporated into the RLS. The final analysis, after the record linkage and examination of dosimetry records for linked workers, was based on data from 161 male workers (82 fathers of cases and 79 fathers of controls) and 18 female workers (15 mothers of cases and 3 mothers of controls).

5.5 Since this study was primarily a test of the Gardner hypothesis, the authors attempted to exclude from the main results the West Cumbrian cases on which the Gardner hypothesis was based. The investigators undertook cross-checks which indicated that they had been successful in identifying and excluding the cases included in Gardner's study.

5.6 Analyses were carried out comparing the risk of cancer in the children of workers on the NRRW with that in children whose parents were not. A relative risk of one means that risks in the two groups were the same.

5.7 The main results are given in Table 5.1; as noted above these results are based on a dataset excluding the Gardner cases. For leukaemia and non-Hodgkin's lymphoma, children of male radiation workers showed a significantly increased relative risk of 1.77. Relative risks were similar for industrial and non-industrial workers. For other cancers, relative risks were close to one. It should be noted that although most cases in this study had a single matched control, those included from the study of Kinlen et al had three. It is thus not possible to draw conclusions simply on the basis of the ratio of the numbers of cases to controls.

5.8 Table 5.1 also shows relative risks by radiation dose category. One relative risk is significantly raised, that for the zero and sub-threshold dose category (<0.1 mSv) of total preconceptional exposure. This is based on six cases and no controls giving a lower confidence limit of 1.18. The relative risk for a total preconceptional dose of 100 mSv or more is less than unity, although not significantly so. None of the relative risks for cancers other than leukaemia and non-Hodgkin's lymphoma is significantly different from unity.

5.9 The authors also looked at dose treated as a continuous variable (results not tabulated here; see Draper et al, 1997b). No significant dose–response relationship was found for any of the diagnostic groups or exposure periods studied. The possibility of an increased risk of leukaemia or non-Hodgkin's lymphoma following high dose exposure was of particular interest. For this diagnostic group, the estimated average relative risk coefficient over the whole range of preconceptional doses was 1.62 per 100 mSv. This estimate is not significantly different from one, ie it is consistent with a uniform risk not dependent on dose. The value of the estimate is largely determined by the apparently higher risks at lower doses, as shown in the (non-significant) estimates for the two lower dose categories in Table 5.1. When the analysis was repeated taking into account whether individuals were radiation workers ('adjusting for radiation worker status'), the relative risk of leukaemia and non-Hodgkin's lymphoma for a preconceptional dose of 100 mSv was reduced from 1.62 to 0.92. Neither of these relative risks is significantly different from unity. The apparent radiation effect thus appears to be due to a difference between radiation workers and others, and not to differences between radiation workers with different doses.

5.10 The effect of including the cases of Gardner et al in this study was also examined (results tabulated in Draper et al, 1997a,b); the broad conclusions were unaffected.

5.11 Relative risks for the children of female radiation workers are also shown in Table 5.1. For these children, childhood leukaemia and non-Hodgkin's lymphoma showed a non-significantly raised relative risk of 4.0; for other childhood cancers there was a significantly increased relative risk of 5.5; for all cancers taken together the relative risk was significantly elevated at 5.0. There were no significant trends with any maternal dose variables after adjustment for maternal radiation worker status (Draper et al, 1997b). The observed excess was not concentrated within any one diagnostic group and the authors concluded that the numbers in the study were too small for reliable estimates of the excess risk, if any, to be made.

Nuclear Industry Family Study (NIFS)

5.12 In this study (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 Atomic Energy Authority, British Nuclear Fuels plc (BNFL) 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 with a pension entitlement at the first two.

Table 5.1 Selected results from the Record Linkage Study (cancers under the age of 15 years)

(a) Numbers of linkages to the NRRW and relative risks for categories of childhood cancer

		Cases	Controls†	Relative risk (95% CI)
Fathers	LNHL* excluding Gardner cases‡	40	38	1.77 (1.05–3.03)
	LNHL including Gardner cases	49	44	1.83 (1.11–3.04)
	All other cancers	33	35	0.94 (0.56–1.58)
	All cancers	82	79	1.33 (0.93–1.90)
Mothers	LNHL	4	1	4.0 (0.40–197)
	All other cancers	11	2	5.5 (1.20–51.0)
	All cancers	15	3	5.0 (1.42–26.9)

(b) Relative risks for childhood leukaemia and non-Hodgkin's lymphoma by paternal preconceptional dose categories of radiation exposure, excluding 'Gardner cases' and their controls

Variable	Dose group (mSv)	Cases	Controls†	Relative risk (95% CI)
Total preconceptional dose	<0.1	6	0	8.17 (1.18–∞)
	0.1–	29	32	1.47 (0.81–2.68)
	50–	4	2	4.49 (0.60–52.0)
	≥100	1	4	0.46 (0.01–5.15)
Six months preconceptional dose	<0.1	20	19	1.61 (0.77–3.38)
	0.1–	17	14	2.12 (0.91–5.13)
	5–	1	1	1.73 (0.12–156)
	≥10	2	4	1.33 (0.10–12.8)

* LNHL is leukaemia and non-Hodgkin's lymphoma.
† Note that some cases had three matched controls. Thus it is not possible to draw conclusions from a simple ratio of linkages for cases to those for controls.
‡ Note that analyses excluding 'Gardner cases' are those which exclude cases of LNHL both born and diagnosed in West Cumbria in the years 1952–1985 and their associated controls. These analyses are an independent test of the Gardner hypothesis.

5.13 A total of 46,396 workers were approached and completed questionnaires were received from 36,050 (78%). Cancers before the age of 25 years were reported in 94 children of men who returned questionnaires and in 22 children of women respondents. Five of these children had both father and mother in the survey.

5.14 In order to compare with the general population, standardised incidence ratios (SIRs, see the Glossary) were calculated for children born after 1965; SIRs were reported for offspring at ages 0–24 years, and separately for ages 0–14 years. For all malignancies diagnosed under the age of 25 years, the SIR was 0.98, and the highest reported SIR (1.18) was for leukaemia and non-Hodgkin's lymphoma. For none of the reported disease groupings was the SIR significantly different from unity, either for ages 0–24 years or ages 0–14 years.

5.15 However, the more important analyses compared different groups within the cohort. In order to test the Gardner hypothesis, when considering leukaemia and non-Hodgkin's lymphoma, the investigators presented results excluding cases born in Cumbria before 1986 as well as for all cases. This was because the latter grouping would include the cases which had led to the formulation of the hypothesis.

5.16 Analyses were first carried out simply on the basis of the father's status up to the time of conception of the child, see first column of Table 5.2. The categories considered were 'before employment in the nuclear industry' (used as baseline), 'after employment but not monitored', and 'monitored'. The relative risk for all cancers among children conceived after employment to non-monitored workers was 1.5; for children conceived after the father had been monitored it was 1.4. For LNHL, excluding the Cumbrian cases, the figures were 1.4 and 2.2. None of these rates was statistically significantly elevated.

5.17 Relative risks were also calculated for the various disease groupings, for categories of paternal cumulative preconceptional external dose (see second panel of Table 5.2) and dose in the six month preconception period (third panel). The dose categories selected were similar to those used by Gardner et al (1990). For all disease groupings and dose categories there was a tendency for relative risks to be above one, though few of these were statistically significant, and there were no significant dose response relationships.

5.18 Because of the Gardner hypothesis, particular attention focuses on the results for LNHL excluding Cumbrian cases born before 1986. There were no cases in the children of fathers with preconceptional lifetime doses in the range 50–100 mSv or doses of 5–10 mSv in the six month preconception period. One case fell in the highest dose groups (total preconceptional dose above 100 mSv, 10 mSv in the six months before conception). This gave (non-significantly) elevated relative risks of 4.3 and 7.4, respectively, compared with rates before employment and monitoring. There were nine cases in the lowest dose groups (less than 50 mSv lifetime; less than 5 mSv in the six months before conception). These resulted in relative risks of 2.3 and 2.2, respectively, neither elevation being significant.

5.19 When the Cumbrian cases of LNHL were included, there was a significantly elevated relative risk of 5.4 for the grouping with six month preconceptional doses above 10 mSv; for total preconceptional doses above 100 mSv the elevation was on the borderline of statistical significance**,** but these results must be viewed with caution because of the small number involved.

5.20 There was a tendency for these raised rates in groupings of LNHL to be driven by leukaemia rather than NHL (results not tabulated here).

5.21 There were very few cases in the children of female workers and the investigators presented only a brief analysis. In this, rates in certain categories were compared to those in children before their mothers were employed in the nuclear industry. The relative risk of all malignancies in children conceived after their mother's first employment but before first monitoring was 2.7, a significant elevation. For those conceived after first maternal monitoring the relative risk of all malignancies was elevated (1.5 fold), but not significantly so.

Comparison of NIFS and the RLS

5.22 The NIFS was a study of children of nuclear industry workers. The RLS was a UK population-based case–control study of children with cancer. The two studies were thus of very different design. However, because they are both large investigations that enable further examination of the Gardner hypothesis, it is worth considering the extent to which they are reflecting the same data.

5.23 The NIFS was a retrospective cohort study of children born to workers at AWE, AEA and BNFL. All records were individually linked to the parent's employment and monitoring data, regardless of whether the child had developed cancer or whether the parent had been monitored before the child's conception. The number of cases of childhood cancer identified in the children of the nuclear workers studied was 111.

Table 5.2 Selected results from NIFS: cancers under the age of 25 years in children of male nuclear workers, classified according to paternal employment history before conception, monitoring for radiation exposure, and estimated radiation dose

	All malignancies		LNHL (all cases)		LNHL (excluding Cumbria before 1986)		Other malignancies	
	No. of cases	RR (CI)	No. of cases	RR (CI)	No. of cases	RR (CI)	No. of cases	RR (CI)
Before employment and monitoring	39	1.0	11	1.0	7	1.0	28	1.0
After employment, not monitored	16	1.5 (0.8–2.7)	3	1.0 (0.3–3.6)	3	1.4 (0.3–5.5)	13	1.7 (0.9–3.3)
Monitored	39	1.4 (0.9–2.2)	14	1.8 (0.7–4.4)	10	2.2 (0.7–6.6)	25	1.3 (0.7–2.2)
Cumulative external dose (mSv)								
<50	29	1.4 (0.8–2.2)	10	1.7 (0.6–4.3)	9	2.3 (0.8–7.2)	19	1.2 (0.7–2.2)
50–	4	1.3 (0.5–3.8)	1	1.2 (0.2–9.4)	0		3	1.4 (0.4–4.7)
≥100	6	2.2 (0.9–5.3)	3	3.9 (1.0–15.7)	1	4.3 (0.5–40.5)	3	1.5 (0.5–5.0)
Estimated cumulative dose in six months before conception								
<5	31	1.3 (0.8–2.2)	11	1.7 (0.7–4.3)	9	2.2 (0.7–6.8)	20	1.2 (0.7–2.1)
5–	3	1.4 (0.4–4.5)	0	0.0 (–)	0		3	1.9 (0.6–6.3)
≥10	5	2.5 (1.0–6.5)	3	5.4 (1.4–20.5)	1	7.4 (0.8–66.5)	2	1.4 (0.3–5.9)

5.24 The RLS was a national case–control study of British children diagnosed with cancer under the age of 15 years between 1952 and 1986, controls being selected from birth registers. Once the children were selected for the RLS, details of parents were compared to the NRRW and records were linked in order to identify parents who had been monitored before the child's conception. The total number of cancer cases in the RLS was 35,949, of which 94 had a parent who linked to a NRRW record.

5.25 Investigations showed that only 11 cases of childhood cancer were included in both studies. This limited overlap is largely explained by differences in the two study designs.

5.26 The design of NIFS was such that children of ex-workers who had died, were over 75 years or whose details were not recorded in the pensions database were not available for inclusion in the study. The RLS included children of these workers if their parent had been monitored for occupational exposure or radiation before the child's conception.

5.27 The RLS included cancer cases diagnosed between 1952 and 1986 (plus cases of leukaemia and NHL diagnosed between 1987 and 1990 in Scotland). Children diagnosed over the age of 15 years were not included. The NIFS included cancers diagnosed at any time before 1996 at any age, and reported both analyses of cancers up to age 25 years and cancers up to age 15 years (the latter for comparison with the RLS), though in children of a more restricted workforce.

5.28 The exposure comparison groups in the two studies were necessarily different owing to the study designs. In the NIFS the comparison group consisted of children of parents with no record of monitoring or employment in the three workforces before the conception of the child, but who (by definition) must have worked in the nuclear industry after conception. This is different from the RLS, in which the exposure reference group comprised children of parents not on the NRRW before the conception of the child (almost all of whom would in fact not have been employed in the industry at any time). This difference needs to be considered in the comparison of the results of the two studies.

5.29 The dosimetry in the NIFS was based on annual dose returns as used in the epidemiological analysis of a combined cohort from the nuclear industry (Carpenter et al, 1995). Six month preconceptional doses were estimated by pro-rata scaling, as was the portion of the total preconceptional dose which was received prior to conception in the year of conception. Such scaling for calculation of six month preconceptional dose can be problematic, as high-lighted by an investigation of leukaemia and other cancers in the children of male workers at Sellafield (HSE, 1993). Doses in the RLS were estimated using monthly worker dose records and so are likely to be somewhat more reliable, particularly for six month preconceptional dose. However, total pre-conception doses should be similar in the two studies, and a subsequent comparison of the two studies found this to be so, with one exception. A further consideration is that NIFS used later, and probably more realistic, dosimetry for a subgroup of participants (those employed at Harwell in the 1950s).

5.30 Although there was little overlap between the cases included in the NIFS and the RLS, it should be noted that the overlap of the studies was greater for fathers with high doses. Both NIFS and the RLS reported six fathers with more than 100 mSv PPI; two of these were in common to both studies. Even so, published results for the two studies are in general very similar.

Extended Cumbrian Study

5.31 Parker and co-workers have established a database of all live- and still-births in Cumbria in the period 1950–1989 (later extended to 1991). Childhood cancers were ascertained from a number of sources and reviewed centrally (Dickinson et al, 2001). Within this Cumbrian cohort, children of workers at the Sellafield nuclear plant have been identified (Parker et al, 1997). This database has been used for three studies which are relevant to this report:

(i) a modelling study of the effects of population mixing on childhood cancer rates in Cumbria (Dickinson and Parker, 1999),

(ii) a study of leukaemia and non-Hodgkin's lymphoma in the children of Cumbrian nuclear workers in which an allowance was made for the effects of population mixing (Dickinson and Parker 2002),

(iii) a study of solid tumours in the children of Cumbrian nuclear workers, broadly similar to the LNHL study above (Dickinson et al, 2002).

These studies are described in the following sections.

Modelling the effect of population mixing in Cumbria

5.32 This extended Cumbrian cohort was used for a study of the influence of population mixing on rates of childhood cancer (in particular, leukaemia and NHL) at ages 1–14 years (Dickinson and Parker, 1999). Cases in children aged less than 1 year were excluded because of evidence that many infant leukaemias differ at a molecular level from other childhood leukaemias (see box in Chapter 6 on the causes of leukaemia).

5.33 From 1969 onwards, parents' place of birth have been shown on birth certificates and was available to the investigators. Each child was categorised as having both, one, or neither parent born within Cumbria. These and other data were used to construct indices of population mixing for Cumbrian electoral wards. Analyses of the effects of population mixing on rates of childhood cancer were conducted both at the individual and at the ward level. Children born in Seascale were excluded from this part of the analysis.

5.34 The individual level population mixing indicator was whether both parents had been born outside Cumbria or not. The ward based measure, estimated for five-year periods, was the proportion of all parents within a ward who were born outside Cumbria. This latter measure was standardised to have a range of 0–1.

5.35 Levels of LNHL were significantly raised in children of parents both of whom were born outside Cumbria ('incomers'), relative to other children (RR = 2.3). Rates were similar in children who had one parent born outside Cumbria to those in children with both parents born in Cumbria. At a ward level, there was a significantly elevated level of LNHL in areas with a higher proportion of parents born outside Cumbria. The RR was 6.8 for the ward with the highest observed level of population mixing compared to the ward with the lowest observed mixing. There is an incomer effect within wards, the characteristics of both the individual and the community being important.

5.36 When attention was restricted to acute lymphoblastic leukaemia (ALL) and NHL the excess in wards with the highest levels of population mixing was increased and statistically significant (RR = 11.7). The effect was greater in those aged 1-6 years than in those aged 7–14 years. No effect of population mixing was seen on levels of other sub-types of leukaemia or on solid cancers.

5.37 On the basis of this analysis, Dickinson and Parker formulated a model which expressed the level of ALL and NHL in terms of age (1–6 versus

7–14 years), whether both parents were born outside Cumbria, and the level of community population mixing. Under this model, just over half of the cases of ALL/NHL were attributable to population mixing.

5.38 This model was used to predict the number of cases of ALL/NHL at ages 1–14 years in Seascale. Those considered were children born in Seascale in the period 1950–1989 and diagnosed before the end of 1992. There is some uncertainty in the model predictions because place of birth was not known for all the Seascale parents. However, about three cases are predicted by this model; the confidence interval given in the paper runs from rather more than one case to six. However, this confidence interval refers to the mean of the predicted value. In order to judge the extent to which the population mixing model explains the observed number of cases the observed value should be compared with the interval (a 'prediction interval') that allows for the fact that that there is a statistical distribution associated with this mean. This interval will be wider than the 95% confidence interval presented by Dickinson and Parker, though a quantitative assessment of it is not available.

LNHL in the children of male Sellafield radiation workers

5.39 The extended Cumbrian Birth Cohort database was used to investigate levels of childhood leukaemia and non-Hodgkin's lymphoma (and factors which might affect these levels) in the children of male radiation workers at the Sellafield nuclear plant (Dickinson and Parker, 2002). Radiation workers were those monitored for exposure to radiation at any time before the conception of the child in question. Comparisons were made with children born outside Seascale and whose fathers had never worked at Sellafield (the 'non-Sellafield non-Seascale cohort').

5.40 Because of the known excess of LNHL in Seascale, analyses were presented for the children of radiation workers living in Seascale and for children of radiation workers living outside Seascale as well as for all radiation workers combined. The analysis included the cases in the Gardner study.

5.41 The effects of demographic variables (parents' place of birth, community population mixing, sex, birth order, singleton/multiple births and social class) were modelled using data from the non-Sellafield non-Seascale cohort. The effect of preconception irradiation was estimated taking into account the effect of demographic variables modelled in this way. Full population mixing data were available only after 1968. Prior to this population mixing data were available only for 7% of births (68% in Seascale). Analyses adjusting for population mixing were carried out for Seascale births separately for calendar periods 1950–1968 and 1969–1991, but for non-Seascale births only for 1969–1991.

5.42 Estimates of radiation dose in the total preconception period were made pro-rata from recorded annual doses.

5.43 When children of all radiation workers were compared with those of the non-Sellafield non-Seascale cohort (without demographic adjustment) (see Table 5.3), the relative risk of LNHL was 1.9, which was on the borderline of statistical significance. For the children of radiation workers who lived in Seascale the relative risk was 9.2 (highly significant); for non-Seascale radiation workers the RR was 1.1 (not significant). The excess in the children of Seascale radiation workers was greater in the younger age group, 0–6 years, for whom the RR was about 15 (highly significant). When adjustment for demographic variables was made for those born between 1969 and 1991 (and taking the full age range, 0–24 years), the relative risks for the children of all radiation workers changed little. However, for the children of radiation workers living in Seascale the RR fell from 9.8 to 3.9 (no longer a significant elevation).

Table 5.3 Extended Cumbrian Study: comparison of rates of leukaemia and non-Hodgkin's lymphoma to age 25 years

	Comparisons of radiation worker and non-Sellafield/non-Seascale cohorts								
	All radiation workers			Non-Seascale radiation workers			Seascale radiation workers		
Diagnostic group	**RR**	**(95% CI)**	**p**	**RR**	**(95% CI)**	**p**	**RR**	**(95% CI)**	**p**
(a) Unadjusted									
Age 0–6 Born: 1950–68	3.3	(1.3–7.0)	0.02	1.8	(0.4–4.9)	0.35	14.9	(3.6–40)	0.001
1969–91	1.4	(0.4–3.9)	0.56	0.5	(0.0–2.3)	0.46	15.4	(2.5–50)	0.008
1950–91	2.3	(1.1–4.3)	0.03	1.1	(0.3–2.7)	0.83	15.0	(5.3–33)	<0.0001
Age 7–24 Born: 1950–68	1.8	(0.5–4.2)	0.31	1.5	(0.4–4.0)	0.53	4.1	(0.2–18)	0.26
1969–91	0.0	–		0.0	–		0.0	–	
1950–91	1.3	(0.4–3.1)	0.62	1.1	(0.3–2.9)	0.89	3.1	(0.2–14)	0.34
Ages 0–24 Born: 1950–68	2.4	(1.2–4.4)	0.02	1.6	(0.6–3.4)	0.28	9.0	2.8–21	0.001
1969–91	1.0	(0.3–2.8)	0.95	0.4	(0.0–1.7)	0.24	9.8	1.6–31	0.02
1950–91	1.9	(1.0–3.1)	0.05	1.1	(0.5–2.2)	0.80	9.2	(3.6–19)	0.0001
(b) Adjusted for effects of demographic variables									
Age 0–6 Born: 1969–91	1.5	(0.4–4.1)	0.53	0.6	(0.0–2.9)	0.62	4.6	(0.7–15)	0.09
Age 0–24 Born: 1969–91	1.1	(0.3–2.8)	0.92	0.4	(0.0–1.9)	0.34	3.9	(0.6–12)	0.12

Table 5.4 Extended Cumbrian study: trend of childhood leukaemia and non-Hodgkin's lymphoma with father's dose

Relative risk per 100 mSv of father's total preconceptional external radiation dose

	All births				Non-Seascale				Seascale			
Diagnostic group	**No. of cases**	**RR**	**95% CI**	**p**	**No. of cases**	**RR**	**95% CI**	**p**	**No. of cases**	**RR**	**95% CI**	**p**
(a) Unadjusted												
Age 0–6 Born: 1950–68	6	1.9	(1.1–2.6)	0.03	3	1.8	(0.8–2.9)	0.13	3	2.1	(0.9–3.6)	0.08
1969–91	3	1.2	(0.3–2.7)	0.79	1	–	–	–	2	1.8	(0.3–5.2)	0.40
1950–91	9	1.7	(1.0–2.4)	0.04	4	1.7	(0.7–2.7)	0.21	5	2.1	(1.0–3.3)	0.06
Age 7–24 Born: 1950–68	4	1.3	(0.3–2.4)	0.61	3	1.2	(0.2–2.5)	0.80	1	–	–	–
1969–91	0	–	–	–	0	–	–	–	0	–	–	–
1950–91	4	1.3	(0.3–2.4)	0.63	3	1.2	(0.2–2.5)	0.82	1	–	–	–
Age 0–24 Born: 1950–68	10	1.7	(1.0–2.3)	0.04	6	1.6	(0.8–2.4)	0.17	4	2.1	(0.9–3.3)	0.06
1969–91	3	1.2	(0.2–2.6)	0.83	1	–	–	–	2	1.8	(0.3–5.1)	0.43
1950–91	13	1.6	(1.0–2.2)	0.05	7	1.5	(0.7–2.3)	0.26	6	2.0	(1.0–3.1)	0.04
(b) Adjusted for effects of demographic variables												
Age 0–6 Born: 1950–68	–	–	–	–	–	–	–	–	3	2.0	(0.9–3.4)	0.08
1969–91	3	1.4	(0.2–3.1)	0.60	–	–	–	–	2	2.1	(0.4–5.9)	0.31
Age 0–24 Born: 1969–91	3	1.4	(0.2–3.1)	0.62	1	–	–	–	2	2.1	(0.4–5.9)	0.31

Note: includes Gardner cases

5.44 Tests were carried out within the radiation worker cohort for a trend in the risk of LNHL with increasing preconceptional dose (see Table 5.4). Before any demographic adjustment was made there was an association between LNHL and total PPI dose (RR = 1.6 per 100 mSv) which was on the borderline of statistical significance. This was based on 13 cases (9 in the 0–6 years age group) of which 11 were cases reported by Gardner *et al* and 12 were included in the HSE study. The estimated RR for Seascale was 2.0 per 100 mSv (significant) while that outside Seascale was 1.5 (not significant). Adjustment for demographic factors made little difference to the estimated relative risk but this could be calculated only for the two cases in Seascale in 1969–91 and the estimate was then not close to statistical significance. The RR estimated by Dickinson and Parker in this study may appear lower than that reported by Gardner et al (6.4 for the children of fathers receiving a total preconceptional radiation dose of 100 mSv or more). However, these figures are not directly comparable, because the Gardner estimate relates to the risk for workers in the highest dose group, ie with preconceptional doses above 100 mSv, whereas the Dickinson and Parker estimate is the average increase in RR per 100 mSv over the dose range for radiation workers.

Solid tumours in the children of male Sellafield radiation workers

5.45 Dickinson et al (2002) also studied solid tumours, excluding those which are gender-specific, in the same cohort as was used for the LNHL study. Subgroupings of disease were also considered:

(i) Hodgkin's disease,

(ii) brain and spinal tumours,

(iii) other (non-gender-specific) solid tumours.

Eighteen cases of cancer occurred in the children of radiation workers and 335 cases in the children of other residents of Cumbria. Comparisons were made between rates of cancer in children of radiation workers and rates in children whose fathers had never worked at Sellafield. In most instances the relative risks were above one, but none of them reached statistical significance. For the grouping of all solid tumours (excluding gender-specific tumours) over the age range 0–24 years the relative risk was 1.5. For the subgrouping of Hodgkin's disease the relative risk was 1.4, for brain and spinal tumours 0.9, and for other (non-gender-specific) solid tumours 1.9.

5.46 Data to allow adjustment for population mixing were not available for births before 1969 except in Seascale. In contrast to the LNHL analysis, calendar periods before and after 1969 were not considered separately. Instead, an analysis was undertaken for the category 'other (non-gender-specific) solid tumours' in which the whole calendar period was considered and missing data were imputed. The relative risks were little affected.

5.47 Within the children of radiation workers there was no evidence for an increased risk of cancer with increasing paternal preconceptional radiation dose. The relative risk per 100 mSv was 0.5 (not significant).

US 'Three Site Study'

5.48 This was a case–control study of childhood cancer around three Department of Energy nuclear facilities in the USA (Sever et al, 1997). The nuclear facilities studied were Hanford, Idaho National Engineering Laboratory (INEL) and the K-25, Y-12 and X-10 plants at Oak Ridge. Hanford site and INEL operated nuclear reactors and reprocessed fuel to obtain plutonium. The first two of the Oak Ridge plants were concerned with uranium enrichment by gaseous diffusion and electromagnetic separation, respectively. X-10 was the code name for Oak Ridge National Laboratory itself where a variety of nuclear research was undertaken. The main aim of the Three Site Study was to test the Gardner hypothesis.

5.49 The categories of cancer studied were:

leukaemia

leukaemia and non-Hodgkin's lymphoma

cancers of the central nervous system

and, in addition, all these cancers combined. Cases of the specified types of cancer occurring prior to age 15 years in counties surrounding these three facilities in the time period 1957–1991 were assembled using multiple sources. Attention was restricted to cases whose parents were resident in these counties at the time of their birth.

5.50 A total of 233 cases were identified; 28 of these had fathers employed at a study site, and 10 had mothers employed at a site. Two types of control were selected: 'unrestricted' and 'restricted' controls. The former were children born in and residing in the study area for at least as long as the case. The restriction applied to the latter was that, in addition, the father must have worked at one of the facilities included in the study prior to the child's conception. The restricted controls were used for the analyses involving categories of radiation exposure.

5.51 For all facilities combined, there was no preferential tendency for cases to have fathers employed at a nuclear site (Table 5.5). When the three facilities and diagnostic groupings are considered separately, the only relative risk exceeding unity is for tumours of the central nervous system (CNS) at Hanford (RR = 2.5) and it is not statistically significant. This part of the analysis used the unrestricted controls.

5.52 For mothers, the numbers are smaller. However, the relative risk for CNS tumours at Hanford is similar to that for fathers (RR = 2.57, not significant). The Hanford data drive a similar excess for CNS tumours when all three facilities are combined, although this is still not statistically significant.

5.53 Potential confounders such as maternal age, number of prior live births and birth weight did not affect the results.

5.54 There was no suggestion of an association between childhood cancer and exposure to internal emitters, a non-zero neutron or tritium dose or a non-zero maternal dose prior to conception or during gestation.

5.55 The distribution of total preconceptional dose to fathers of cases and controls at the three facilities is given in Table 5.6. It is notable that doses to the fathers of controls are higher than those to the fathers of cases.

5.56 Sever et al present both an analysis by dose category and one in which dose is treated as a continuous variable and the relative risk is estimated using a linear model. Calculations are presented separately for Hanford (which contributes most of the information) and for all three facilities combined. The results of the linear modelling are in Table 5.7. Only for leukaemia at Hanford does the relative risk exceed unity (RR = 1.93), but it is not statistically significant and the 95% confidence interval is very wide.

German study of childhood cancer

5.57 Michaelis and co-workers have conducted a large case–control study of cancer in children under the age of 15 years in Germany (Meinert et al, 1999). This study included 1184 cases of childhood leukaemia, 234 non-Hodgkin's lymphoma and 940 solid tumours, together with 2588 controls. This investigation was able to consider a variety of risk factors including lifestyle and environmental factors.

Table 5.5 Three Site Study: employment of fathers of cases and unrestricted controls prior to conception at three sites combined by diagnosis

	Diagnosis			
Employment	**Leukaemia**	**LNHL**	**CNS**	**All cancers**
Total cases	132	158	75	233
Father EPC	14	16	12	28
Proportion EPC	0.11	0.10	0.16	0.12
Total unrestricted controls	528	632	300	932
Father EPC	61	82	53	135
Proportion EPC	0.12	0.13	0.18	0.14
Relative risk (95% CI)	0.90 (0.46–1.73)	0.73 (0.40–1.33)	0.86 (0.40–1.85)	0.77 (0.48–1.24)

EPC = 'employed at the facility of interest prior to conception'.
After Table 7 of Sever et al (1997).

Table 5.6 Three Site Study: distribution of subjects included in dose-response analyses by total dose received by the father prior to conception – all cancers

	Site							
	Hanford		**Idaho**		**Oak Ridge**		**All sites combined**	
Dose category (mSv)	**Cases**	**Controls**	**Cases**	**Controls**	**Cases**	**Controls**	**Cases**	**Controls**
0	1	7	2	7	5(4*)	25(20)	8(4)	39(20)
<1	6	19	1	0	2	5	9	24
1–	7	38	0	2	1	5	8	45
10–	2	16	0	1	0	0	2	17
50–	1	1	0	2	0	1	1	4
100+	0	3	0	0	0	1	0	4
Total	17	84	3	12	8	37	28	133
Mean dose[†] (mSv)	7.1	14.4	0.16	15.1	0.26	5.4	4.4	12.0

***** Number of unmonitored cases or controls. For Hanford unmonitored could not be distinguished from recorded doses of zero.
[†] Unmonitored cases and controls were assumed to have doses of zero.
After Table 14 of Sever et al (1997).

Table 5.7 Estimates of relative risk and 95% confidence intervals for study childhood cancers as a result of a dose of 100 mSv received by the father prior to conception for Hanford and the three study sites combined based on a linear model RR = 1+β dose

	Diagnosis			
DOE site	**Leukaemia**	**LNHL**	**CNS**	**All cancers**
Combined	0.73 (<0.73–7.6)	0.75 (<0.75–3.5)	0.22 (<0.22–3.6)	0.75 (<0.75–2.1)
Hanford	1.93 (<0.1–29)	0.75 (<0.75–6.5)	0.22 (<0.22–8.1)	0.75 (<0.75–3.3)

After Table 17 of Sever et al (1997).

5.58 Particular interest attaches to the examination of the Gardner hypothesis in this large German investigation. The highest preconceptional doses to the workers in the German case–control study were less than 30 mSv and, as such, below the level of 100 mSv at which Gardner reported an excess of leukaemia in offspring. The relative risk for fathers of leukaemia cases who were monitored for exposure to ionising radiation before conception of the child was elevated (RR = 1.80), but not significantly so. For NHL, the RR was 0.49, but this was not significantly below one.

5.59 For mothers, analyses were conducted for both occupational and diagnostic radiation exposures during pregnancy and in the 12 or 15 months before conception. The only significant finding was a relative risk of 3.87 for NHL occurring in the child, associated with occupational exposure during pregnancy. There were, however, very few relevant exposures during pregnancy: seven cases and seven controls. There was no evidence for an increased risk connected with diagnostic X-rays in early childhood. Indeed, for children receiving the lowest such exposures there was a statistically significant negative association with leukaemia. However, the authors warn against reading too much into this observation which may have been due to control parents incorrectly dating X-ray examinations of their children.

Study of leukaemia near La Hague

5.60 Pobel and Viel (1997) conducted a case–control study of leukaemia in young people up to the age of 25 years living within 35 km of the La Hague nuclear fuel reprocessing plant. The study included 27 cases of leukaemia diagnosed in the period 1978–1993 and 192 controls. A number of potential environmental and occupational risk factors were considered, including parental occupational exposure to radiation.

5.61 Pobel and Viel conducted a number of analyses. They gave most prominence to an increased trend of leukaemia with use of local beaches by children and by mothers. When those who used the beaches more than once a month were compared with those who used them less frequently the relative risk for children was 2.87 (CI = 1.05–8.72); for mothers the RR was 4.49 (CI = 1.52–15.2). Various other factors also gave positive associations. For children these were: consumption of local fish and shellfish, drinking well water, use of hair dryers, and living in granite houses or on granitic areas. Only the last of these was statistically significant. However, Little (1999) has noted the possibility that selection bias, recall bias and, as multiple statistical testing was carrried out, chance might account for the results (Clavel and Hémon, 1997; Law and Roman, 1997; Viel, 1997; Wakeford, 1997).

5.62 Various types of occupational exposure by fathers and by mothers showed no association with leukaemia. In particular, no fathers of cases (out of 27) had recorded occupational exposure to ionising radiation before conception; for control fathers the numbers were 19 out of 188 (the authors noted that dosimetry could not be obtained in a few cases). Pobel and Viel noted that doses at La Hague were probably lower than at Sellafield.

Childhood malignancies in the offspring of women irradiated for haemangiomas

5.63 Källén et al (1998) studied the offspring of a group of about 18,000 Swedish women treated with radiotherapy for skin haemangioma in childhood (before the age of 18 months). Estimates of radiation dose were available from treatment planning records. The health of a total of about 19,500 of their children was determined using health registers. Comparisons were made with national rates of childhood cancer and tests for trend with dose were carried out.

5.64 A total of 45 childhood malignancies were observed in the offspring of these Swedish women. This was lower, but not significantly so, than the

number expected on the basis of national rates (50.6). There was no evidence for a trend in the rate of childhood cancer with the mother's ovarian dose.

Cancer in the children of cancer survivors

5.65 In our Fourth Report we noted that many children and young adults who develop cancer are now successfully treated and go on to have children of their own. The treatment will often involve the use of ionising radiation or chemotherapy with cytotoxic drugs or both. Investigations of cancer in the children of these cancer survivors thus offer the prospect of throwing light on any effect of irradiation of the parents. Such investigations must, however, separate any effects of radiation from those of chemotherapy. Radiation doses are likely to have been very-non-uniform across the body and efforts are likely to have been made to minimise gonadal doses where this is possible; this will reduce the power of the studies. A further, and very substantial, problem is that genetic predisposition plays a large part in at least some forms of childhood cancer and this must also be allowed for.

5.66 A number of reports concerning such survivors and their children have been published. These include a large study from Scandinavia (Sankila et al, 1998) and studies in the USA and elsewhere have been reviewed (Byrne, 1999). Once allowance for genetic susceptibility has been made, these studies do not provide evidence for a link between PPI and childhood cancer. However, because of the difficulties referred to above, we remain of the opinion that evidence from this kind of investigation is weak.

CHAPTER 6

CHILDHOOD CANCER AND PARENTAL IRRADIATION: DISCUSSION

6.1 Although in general radiation workers receive radiation doses that are comparable with those received by the general public from natural radioactivity in some parts of the UK, they constitute a group of special interest as far as the heritable effects of radiation are concerned. This is because they include members whose gonads (ie testicles and ovaries) may be exposed to doses well above those of the average resident of the UK. The explanation for this is that a major part of the environmental exposure of the general population is due to radon gas, which results in little or no radiation dose to the gonads. For this reason, it is important to establish that the health consequences in the children of radiation workers are consistent with current estimates of radiation risk. If this is the case then there is some reassurance that current occupational radiological protection measures are not seriously flawed. At the outset, however, it should be noted that while there is strong evidence linking irradiation of the fetus during pregnancy with subsequent childhood cancer (see paragraph 6.3), there is little evidence that the radiation received by survivors of the atomic bombs on Hiroshima and Nagasaki led to cancer in their children (see Little et al, 1994, for a review). It is these atomic bomb survivors who provide the most important single source of evidence on the carcinogenic effects of radiation.

6.2 Examination of the cancer mortality among occupationally exposed workers in the nuclear industry has shown that they are at less risk of dying from cancer than the general population (a phenomenon observed with many other industries and known as the 'healthy worker effect'). There is nevertheless an increasing trend with dose (at borderline levels of statistical significance) in mortality from leukaemia in radiation workers, an observation that is consistent with expected levels using current radiation risk estimates. Now, for the first time, we have access to data on the incidence of cancer in the children of a large population of radiation workers and can examine the effect of their exposure to radiation on their offspring.

6.3 In principle, effects in the children of radiation workers could result from unrecognised pathways of exposure of the children themselves, through their parents (including exposure during pregnancy) or from a preconceptional effect through irradiation of the parent's gonads. It is now reasonably well accepted that low doses of ionising radiation from diagnostic examinations received by the fetus during pregnancy can cause cancer in childhood. This finding was originally due to Alice Stewart (Stewart et al, 1958) and has been extended, using additional data, by Bithell and Stewart (1975). A review by Doll and Wakeford (1997) suggests that radiation doses of the order of 10 mGy received by the fetus *in utero* increase the risk of childhood cancer, and that at this level of exposure the excess absolute risk coefficient is approximately 6% per gray, although the exact value of this risk coefficient remains uncertain.

6.4 There is no reason in principle why a mutation conferring predisposition to either leukaemia or lymphoma should not be induced in parental gonads by

radiation and transmitted to the offspring. However, with current understanding of the number of genes likely to be involved in leukaemia and the rate at which potential leukaemogenic changes at those genes might occur in irradiated cells, we would *a priori* expect the probability of such an effect to be extremely low, well below the level at which it could be detected in epidemiological studies of exposed populations. When the COMARE Fourth Report was published in March 1996, only Nomura and his colleagues had apparently demonstrated such a phenomenon in the offspring of male mice, whereas several other studies had failed to do so. Moreover, the need for concurrent controls had become clear in one of these other studies and the apparent failure to use concurrent controls in some of Nomura's early work made assessment of the results problematical. We now understand that, although his publications have not made this clear, concurrent controls were employed in most of the early studies undertaken by Nomura and in all his studies conducted after 1977. Moreover, Daher et al (1998), with one of Nomura's strains, has since confirmed the induction of leukaemia in the offspring of irradiated male mice.

6.5 These positive reports of paternal preconceptional radiation on leukaemia risk in mice cannot be explained in terms of conventional mutations directly induced by irradiation of the germ cells of the male parent. Speculation has included epigenetic effects (see the Glossary) or amplification of the initial irradiation effect due to the induction of genomic instability. Recent work with mice other than the strains used by Nomura, documented and discussed in Chapter 4 of this report, has consistently failed to demonstrate any increase in cancer incidence in the offspring of irradiated mice. If Nomura's results are accepted, the effect is clearly strain dependent. Even so, the radiation risk implied by these animal experiments is too small by at least an order of magnitude to account for the excess of childhood leukaemia observed in Seascale. We note that Nomura concurs with this conclusion. Therefore, we conclude that animal studies provide no evidence to suggest that the irradiation of paternal gonads at dose levels to which workers in British nuclear industries have been occupationally exposed (a maximum total dose of around 1 Sv prior to conception and usually well below this) is likely in itself to result in an increased risk of leukaemia or lymphoma in their children.

6.6 So far our discussions of paternal preconceptional radiation have been driven largely by the need to explain the raised incidence of childhood leukaemia and NHL in Seascale. However, even before the publication of the study of Gardner et al, we were concerned to examine the health of children of employees in the nuclear industry and had recommended the commissioning of two major studies, the Record Linkage Study (RLS) and the Nuclear Industry Family Study (NIFS). In addition, information about large-scale studies in the USA and Germany has since become available together with studies of LNHL and solid tumours in Cumbrian born children of radiation workers. We now have information about the children of a large proportion of radiation and non-radiation workers in the nuclear industry in the UK (and also important data from overseas) and therefore pose the following more general questions.

(i) Is there an enhanced frequency of childhood leukaemia, non-Hodgkin's lymphoma (NHL), or any other childhood malignancy among the offspring of radiation workers?

(ii) If so, is the excess related to radiation dose?

6.7 A preconceptional effect through exposure of fathers' sperm and their precursor cells in the testicles was postulated by Gardner et al (1990) to explain the apparent dose-related increase in childhood leukaemia in his case–control study of the children of Sellafield workers. However, no increase was observed

in the offspring of Japanese atomic bomb survivors or in the offspring of Scottish or Ontario nuclear industry workers. Indeed, in the two latter studies the relative risk was less than one (ie the children had *lower* than expected rates of leukaemia), although this was not statistically significant. These matters have been discussed in some detail in the COMARE Fourth Report which deals with the evidence available up to 1992. Do any of the more recent studies provide any evidence that exposure to radiation of workers in the nuclear industry is responsible for an increased risk of childhood cancer in their offspring?

Recent epidemiological studies

6.8 A large and well-conducted study of the children of workers at three nuclear sites in the USA has recently become available. This also does not support the hypothesis of a link between total paternal preconceptional dose and childhood leukaemia/NHL. The relative risk of LNHL per 100 mSv in the children of nuclear workers in this study was 0.75, which did not differ significantly from one. Detailed dose records were not available to test shorter preconception periods (eg three months). The study does not support a general application of the Gardner hypothesis nor does it suggest a generalised, non-dose-related increase in levels of childhood cancer in the children of radiation workers, which is a possible interpretation of some other studies (see below). We note, however, that relatively few of the workers in the US study had received doses comparable with those experienced by the most highly exposed UK workers, in particular those at Sellafield during its first two or three decades.

6.9 Pobel and Viel (1997) conducted a case–control study of leukaemia in young persons up to the age of 25 years in the region around the La Hague nuclear fuel reprocessing plant. They reported an association between leukaemia and use of the local beaches by mothers and by children. They concluded 'There is some convincing evidence in childhood leukaemia of a causal role for environmental radiation exposure from recreational activities on beaches. New methods for identifying the environmental pathways, focussing on marine ecosystems, are warranted'. However, COMARE, in our Fourth Report, carefully considered the possibility of unrecognised environmental pathways and other sources of uncertainty in dose estimates. We concluded (paragraph 9.16 of our Fourth Report) that the estimated doses to the Seascale population were far too small to account for the observed excess of cases of LNHL on the basis of present knowledge. We see no reason to change this conclusion. Little (1999) included the study of Pobel and Viel in a review of the epidemiology of childhood cancer and also concluded that other factors might account for the observations.

6.10 We note that Pobel and Viel found no evidence of a link between PPI and leukaemia in their children (no case fathers out of 27 had been exposed; 19 control fathers out of 188 had been exposed). This provides further evidence against the idea that such an association is a general phenomenon.

6.11 Källén et al (1998) conducted a cohort study of about 18,000 Swedish women irradiated in infancy for haemangioma. They found no evidence for a link between such irradiation and childhood cancer in the offspring of the women many years later. It is noteworthy that an increased cancer risk has been reported in the women themselves.

6.12 Nowadays, many children and young adults who develop cancer are successfully treated. Many of these treatments involve radiotherapy. If a PPI effect is real, it might manifest itself as an elevated risk of cancer in the offspring of such survivors of childhood cancer. However, a complicating factor is that some childhood cancers have a strong hereditary component; moreover, patients with these diseases frequently also have chemotherapy. It is

difficult to allow for such hereditary influences, but there is no convincing evidence for a PPI effect. We are of the opinion that only weak evidence can be obtained from this kind of study.

6.13 The Record Linkage Study (RLS) and the Nuclear Industry Family Study (NIFS) were designed to approach the question in different ways and their results are not easily compared. Comparison with controls in the same working environment is in some respects preferable to comparisons with the general population but this was not part of the design of the RLS. On the other hand, the NIFS allows exposed workers to be compared with non-exposed workers among the same work forces. This is an important point to note because it is possible that there are differences in lifestyle and habits between workers in the nuclear industry and the general population that could influence childhood cancer rates. The NIFS found that cancer incidence in the offspring of workers in those parts of the nuclear industry in the study was similar to that in the general population, both for leukaemia and for all malignancies. However, there was a suggested, though non-significant, effect if the comparison was made within the same workforce: children of men who had been monitored for external and internal radiation had a relative risk of 1.8 (95% CI 0.7–4.4) for leukaemia and NHL compared with children conceived before their fathers had joined the workforce or had been monitored for radiation.

Relative risk

6.14 Despite their different designs the NIFS and the RLS agree in finding an increased risk (around two-fold) of leukaemia and NHL among offspring of radiation workers. We have seen that the cases in these two studies are to a large extent non-overlapping and the results may be regarded as largely independent. In the case of the RLS the excess in radiation workers is statistically significant but it is not dependent on radiation dose and is essentially determined by an excess among those radiation workers whose occupational dose was too small to measure. In the NIFS, the excess of LNHL in the children of radiation workers generally is non-significant. The only significant excess is in the highest dose group which contains only three cases. When children born in Cumbria before 1986 were excluded, on the grounds that they were likely to include cases in the Gardner paper that had generated the study, the highest dose group contained only one case and the excess was no longer statistically significant. For all childhood cancer taken together (where case numbers are higher) the NIFS reported a 1.5-fold increased risk in the children of both radiation workers and non-radiation workers. None of these figures, however, was statistically significant.

6.15 The study of Dickinson and Parker (2002) found a similar increased risk of leukaemia and non-Hodgkin's lymphoma on the borderline of statistical significance among the children of male radiation workers in Cumbria. In a companion study, Dickinson et al (2002) found little evidence of a PPI effect on solid tumours.

6.16 A recent German case–control study has also found that the relative risk for fathers of leukaemia cases who had been monitored for exposure to ionising radiation before conception of the child was similarly elevated, but not significantly so (relative risk 1.8, 95% confidence interval 0.71–4.58, Meinert et al, 1999).

6.17 To put these figures into some sort of perspective we note that Gardner et al reported relative risks of up to 3.2 for the children of men employed in various other industries and also relative risks below one. Similar findings have been reported elsewhere (Colt and Blair, 1998); all these findings may be due to chance. The authors of the RLS concluded, of their study, that 'If there is any increased risk for the children of fathers who are radiation workers it is small in

absolute terms: in Britain the average risk by age 15 years is 6.5 per 10,000; our best estimate is that the increase is 5.4 per 10,000'. We also note that the NIFS did not detect any increase in incidence of leukaemia or all cancers among children born of nuclear industry employees (which included non-nuclear workers) since 1965 in comparison with the general population in England and Wales.

Association with parental preconceptional dose

6.18 The excess of childhood leukaemia/NHL found among the offspring of radiation workers in the British and German studies could in principle be attributable either to some work-related factor such as radiation exposure, or to some other aspect of life-style, or to some factor associated with population mixing. To focus more specifically on radiation one may ignore comparisons with other groups and seek to establish whether the frequency of childhood leukaemia/NHL is related to the dose of radiation received by the parents before conception of the child. The RLS found that there was no proportionality between the radiation dose received by the fathers and the risk of cancer in their offspring. In fact when the Gardner cases were excluded, the RLS found an inverse correlation, ie the children of those with the highest paternal doses had a lower risk than the children of those whose fathers, though radiation workers, had received doses too low to measure.

6.19 The NIFS found no significant relation to fathers being monitored for radiation exposure prior to conceiving offspring and there was no statistically significant trend for preconceptional dose. The relative risk of LNHL in the children of radiation workers who had received a total preconceptional dose of more than 100 mSv was 3.9. When children born in Cumbria prior to 1986 were excluded (ie removing all potential Gardner cases) only one case remained and the relative risk was 4.3. However, neither of these elevations was statistically significant. The RLS, in contrast, found a decreased risk among the children of fathers who had received more than 100 mSv total preconceptional dose. Thus, while we cannot exclude the possibility that radiation is involved in the NIFS result, it may be a chance finding particularly in the light of the opposite result found in the RLS.

6.20 The Dickinson and Parker study (2002) of all live-born children born in the period 1950–1991 to mothers living in Cumbria covers the ground trodden by the studies of Gardner et al and the HSE (1993, 1994). However, the Dickinson and Parker study is of cohort design and includes an extra case not included in the HSE study. The findings are not independent of those of the Gardner team, but they are consistent with the results reported by them. Dickinson and Parker, in a dose–response analysis with three more cases than that of Gardner et al, found a trend on the borderline of statistical significance for the risk of leukaemia and non-Hodgkin's lymphoma in relation to the father's total preconceptional dose of ionising radiation. The three extra cases by themselves yielded a positive but non-significant association between childhood LNHL and paternal preconceptional dose. These observations, together with those in the earlier studies by HSE and the NIFS, lessen the possibility that the PPI association in Seascale reported by Gardner et al was an anomaly due to, for example, biased choice of controls and somewhat lessen the probability that it was a chance finding.

6.21 All three studies (Gardner, HSE and Dickinson and Parker) illustrate the fact that the risk of childhood LNHL in Seascale was heavily concentrated among the offspring of fathers with high PPI doses. The analyses of Gardner and of HSE found a steep and statistically significant increase in levels of LNHL with PPI dose. There is little support from other studies for the idea that this is a general phenomenon. Dickinson and Parker undertook a different type of analysis which indicated a much less marked increase in LNHL with dose

(indeed it was on the borderline of statistical significance). We understand (personal communication) that collaborative work between Drs Parker and Dickinson and Mr Hodgson of the HSE has identified the following reasons for differences between the two studies:

(i) differences in the distribution of offspring-years which are differential with respect to dose category and Seascale birth status,

(ii) differences between analyses using categorical and continuous PPI dose,

(iii) the presence of Seascale controls with PPI over 200 mSv in the Cumbrian, but not the HSE study.

This implies that the more complete workforce data available to the Cumbria study indicate that HSE control sample underestimated the number of high-dose workers in Seascale and consequently gave a higher estimate for the dose response. The dose response modelled by Dickinson and Parker appears to be inconsistent with the observation that no cases occurred in children of radiation workers in the lowest dose group in Seascale – but both this and the discrepancies between the results of the different analyses can reasonably be ascribed to the general problems of statistical analyses based on very small numbers. We think it unlikely that these difficulties can be resolved by further analysis. Parker and Dickinson and HSE (personal communication) agree that no simple model adequately fits the data for Seascale cases.

6.22 We note that although the HSE study found no evidence for any association with PPI dose for children born outside Seascale, Dickinson and Parker in an unadjusted analysis found an association, albeit smaller and not statistically significant, in their West Cumbria cohort when Seascale-born children were excluded. Indeed, Dickinson and Parker found no statistically significant difference between the dose responses for children born in or outside Seascale, although the study involved numbers too small for firm conclusions to be drawn. The difference between the two studies appears to be largely due to:

(i) differences in the estimates of the numbers of offspring-years at risk in different categories,

(ii) an additional non-Seascale case with high PPI dose in the Cumbria cohort (which covered a longer case ascertainment period); this case was not a death and did therefore not appear in the HSE study which was based on mortality.

In the absence of statistically significant evidence from either study for a PPI effect in West Cumbria outside Seascale, we do not consider it profitable to subject it to further speculation.

Is there a paternal preconceptional radiation effect specific to Seascale?

6.23 Both experimental studies with animals and epidemiological studies outside Cumbria indicate that childhood cancer as an effect of paternal preconceptional radiation is not a general phenomenon, and we have seen nothing to change our opinion on this. The view of COMARE in its Fourth Report was that there was no doubt of an elevated risk of leukaemia and NHL among children and young people living in Seascale. However, the level of risk implied by a preconceptional irradiation explanation, based on experimental and laboratory data, was too small, by at least an order of magnitude, to explain it. The report of Gardner et al, extended by the HSE study, points to a dose-related effect for leukaemia/NHL among children born to radiation workers in the village of Seascale (the analysis by Dickinson and Parker suggests a smaller influence of dose). If a strong dose-response effect in Seascale is not due to chance or confounding by some correlated risk factor, the possibility has to be considered that this village is in some way unique. Radiation workers at

Sellafield, particularly during the 1950s, 1960s, and 1970s, have been among the most highly exposed in the UK nuclear industry (Muirhead et al, 1999), and indeed elsewhere in the West (Cardis et al, 1995). However, these high exposures were far from being limited to those living in the village of Seascale (Parker et al, 1993).

6.24 The Seascale cluster of childhood LNHL and its association has been much studied and no clear understanding has emerged. One possible explanation for the features of the Seascale excess is that it was the play of chance that led to no cases of LNHL in the lowest dose group and that the relatively large number of cases in the medium and high dose groups (three in each) was due to PPI, augmented by some other factor. Alternatively, the association between dose and risk of LNHL might be due to confounding between the level of dose and the level of population mixing or whatever this is a surrogate for. For example, high doses might be correlated with high exposure to infectious agents and both might be related to length of employment at Sellafield. Little is known about the causes of childhood LNHL (see box) and it may be that these are operating, in a way which is effectively chance, to cause the pattern of disease observed.

Causes of leukaemia

Acute lymphoblastic leukaemia (ALL) even in childhood is not a single disease but a mixed group of disorders (Greaves, 1993). Increasing evidence suggests that even sub-types of ALL probably have different causes. Although there is a short interval (four to five weeks) between appearance of the first symptom or sign and diagnosis (Flores et al, 1986; Saha, 1993), the malignant cell line may have begun to proliferate many months before the appearance of symptoms, and it is not clear how long it takes to convert a normal into a malignant cell (Greaves, 1997). A requirement for at least two 'genetic' events appears likely and mutations inherited from either of the parents are considered to account for no more than 5% of all such acute leukaemias (Greaves, 1999).

Evidence from identical twin studies has shown identical gene rearrangements in leukaemic cells that could only have been acquired before birth (Greaves, 1997; Rinaldi et al, 1999). Furthermore, Gale et al (1997) demonstrated unique gene changes in blood of three newborn children who subsequently developed leukaemia. A similar finding was reported by Wiemels et al (1999a). Other molecular studies strongly support the idea that it is a very early event which starts the development of leukaemia (within the first eight weeks of pregnancy). Also it seems that most, if not all, cases of ALL in young children are set off before birth and a significant proportion of the commonest childhood form start off in early pregnancy (Wasserman et al, 1992; Yagi et al, 2000).

The factors which initiate the original genetic change in leukaemia in the first year of life are only partly understood but may include fetal exposure to naturally occurring enzyme (topoisomerase) inhibitors. These are present in a normal diet. Mothers may also express certain genes which prevent the normal breakdown of substances which can damage DNA, the building block of genes. (Ross, 2000; Wiemels, 1999b). In some rare cases it appears that specific changes in the genes of certain blood stem cells leads inevitably to acute leukaemia, but more commonly the causes are less certain. Epidemiological data suggest that an abnormal response to common infection may play a part in the proliferation of a potentially malignant group of cells (Greaves and Alexander, 1993; Greaves, 1999; Kinlen, 2000). Genetic factors have been shown to have an important influence on such reactions (Taylor et al, 1998).

6.25 One factor in which Seascale is unusual, perhaps even unique, is the extent of its incoming population migration. Kinlen has produced considerable evidence that the influx of migrant populations into remote rural areas is associated with an increase in childhood leukaemia that may reflect an infectious aetiology for the disease. He and others have further argued that the population mixing in Seascale has been sufficiently extreme and prolonged that it can explain the excess of childhood leukaemia observed there (Doll, 1999; Kinlen et al, 1995). At the time our Fourth Report was prepared, however, it was unclear what measures of population mixing were relevant and there was little understanding of the quantitative relation of population mixing to the incidence of childhood leukaemia. We considered that population mixing was likely to be a significant contributor to the excess of childhood leukaemia around Sellafield but were not persuaded that it was the whole explanation. We were also conscious of the lack of biological evidence for the infectious agent that was thought to underlie the population mixing explanation. Since that time further research has been published.

6.26 In Chapter 5 we noted a modelling study on the effects of population mixing by Dickinson and Parker (1999). This predicted about three cases of ALL/NHL at ages 1–14 years in Seascale born in the period 1950–1989 and diagnosed before the end of 1992. For the reasons given in Chapter 4, the confidence interval runs at least from one case to six cases and may be wider. We conclude that the variability associated with the predicted value of three cases is such that population mixing is able to explain the whole of the observed Seascale excess (ie six cases). However, the confidence interval would also be consistent with one case (or perhaps no cases) being due to population mixing.

6.27 While the population mixing hypothesis might explain the entire excess, it is possible that other factors may be operating. The possibility of confounding has been mentioned above. Another possibility is that there could be a positive interaction between radiation dose and other factors that might contribute to the high level of childhood leukaemia in Seascale. It must be stressed that there is no evidence for such an interaction and that the hypothesised other factor would have to be present at a higher level in Seascale than elsewhere. Nevertheless it is a fact that four of the five cases of childhood LNHL with fathers having preconceptional exposure greater than 100 mSv were born or lived most of their life in Seascale (Kinlen, 1993; Wakeford and Tawn, 1994). Among the 6 Seascale cases in the HSE and Dickinson and Parker studies whose fathers were radiation workers, none had PPI doses of less than 93 mSv. However, it must be concluded that if population mixing alone were responsible for the Seascale excess, then the concentration of cases in the children of fathers who had received relatively high doses would have to be due to chance or to confounding.

6.28 Population mixing in remote rural areas in Cumbria is not confined to Seascale, although it appears to have been most extreme there. Although Seascale possesses by far the most remarkable excess, there are cases of childhood cancer in other villages near to Sellafield. The excess in Egremont North, for example, has been noted by Craft et al (1993). Among Sellafield workers the paternal preconceptional radiation effect of Gardner et al is seen unequivocally only with those workers whose children lived in the village of Seascale and is not apparent in the offspring of the majority of radiation workers who lived elsewhere, eg in the town of Whitehaven. This raises the question whether population mixing (or whatever this measure is a surrogate for) might have created an environment in Seascale in which the paternal preconceptional radiation effect might be real. We note, however, that the cases in Egremont North are not associated with paternal occupational radiation exposure even

though overall the levels of paternal exposures are larger in Egremont North than in Seascale (Wakeford and Parker, 1996; Wakeford and Tawn, 2000) and population mixing is likely to have been significant here because it was a local centre for mobile construction workers based at Sellafield (Kinlen et al, 1997).

6.29 In our Fourth Report we considered whether the occupational paternal doses could have interacted with some other factor in Seascale to produce an effect sufficiently frequent to account for the increased incidence. We concluded that, whilst the rate of conventional mutation induction by radiation was too low (there would not be enough predisposing mutations with which other factors could interact), we could not exclude the possibility that 'unconventional' changes could interact with, say, viruses (whether latent or exogenous). Since then the evidence for the existence of mechanisms in germ cells leading to frequent radiation-induced changes in certain repeated DNA sequences has become stronger, at least in mice. In Chapter 3 we have also noted that the offspring of irradiated male mice and rats have been demonstrated to have an increased sensitivity to chemical and physical agents. However, there is as yet nothing to connect such changes with childhood cancer. At the same time the nature of the infectious agents hypothesised to underlie the population mixing effect remains unknown. Even accepting the involvement of 'unconventional' phenomena, there are still problems with the idea of a synergistic interaction (Little et al, 1994; Wakeford and Tawn, 2000), although we are not persuaded that these are insuperable. To be tenable, however, the factor (infectious agent?) interacting with paternal radiation exposure would need to be either unique to Seascale or present there at a very much higher level than in any other location that has so far been examined. Moreover, the interaction may need to be more than multiplicative. While unusual, this is not impossible in principle.

6.30 Without considerably greater understanding both of the role of infectious agents in childhood leukaemia and of the processes involved in the 'unconventional' amplification mechanism it would be futile to speculate further. As we stated in our Fourth Report, progress in these areas will depend on high quality innovative basic research and we re-affirm our recommendation that this be fully supported.

Summary of the risks to children of male workers

6.31 A number of epidemiological studies have failed to find evidence for a general PPI effect either among offspring of survivors of the atomic bombs in Japan or of workforces exposed to radiation. We find no convincing evidence to suggest that ionising radiation alone at the doses to which male radiation workers have been exposed results in an increased incidence of childhood cancer.

6.32 On balance, and despite the fact that not all the studies reported statistically significant results, the available evidence indicates that there may be about a two-fold excess of childhood leukaemia and non-Hodgkin's lymphoma among the children whose fathers were radiation workers. There is little evidence for any excess of other malignancies in the children of male radiation workers. Such an excess would be comparable with variations in levels of LNHL reported for the children of other occupational groups. This excess has not been observed outside the UK and Germany and is plausibly attributable to population mixing, perhaps with other socio-demographic or lifestyle factors amongst radiation workers in the UK.

6.33 Some evidence for a dose-related paternal preconceptional radiation effect is a consistent feature of analyses restricted to the village of Seascale, particularly in the early years of the nuclear industry there. We cannot be sure that this is entirely due to chance or to confounding by some other factor

correlated with dose. Current knowledge clearly indicates that the apparent dose response is most unlikely to be due to the exclusive action of preconceptional dose to the fathers. However, possible interaction between paternal preconceptional radiation and some other factor such as that responsible for the population mixing effect cannot be totally excluded.

6.34 We note that doses to current radiation workers are well below those experienced more than 30 years ago.

Children of female workers

6.35 Women comprise a small proportion of those doing radiation work and monitored for radiation exposure and so the number of their children is small in the context of epidemiological studies. Female radiation workers also tend to receive lower doses than do men. However, children of female radiation workers could in principle be exposed during pregnancy at a time when childhood leukaemia can be initiated. They could, of course, also inherit mutations resulting from irradiation of the female germ cells (ova) prior to conception. In our Interim Statement on the Record Linkage Study (RLS) (COMARE, 1998) we noted that the relative risk for all childhood cancers in children whose mothers were radiation workers appeared to be elevated. This observation was based on 15 cases (including 4 LNHL) and 3 controls, giving a relative risk of 5.0 with 95% confidence limits of 1.4–26.9. Examination of the RLS database has shown that the risk does not appear to be associated with exposure during (rather than before) pregnancy (Draper et al, 1997a,b).

6.36 Possible marginally increased risks were reported in both the Nuclear Industry Family Study (NIFS) and the US Three Site Study. The NIFS found a relative risk of 1.5 (not significant) based on two malignancies (no leukaemias) among the offspring of women monitored for radiation exposure. The US Three Site Study found a relative risk of 2.57 for tumours of the central nervous system, although it was not significant (confidence interval 0.85–8.91). The figures in all these studies were, however, based on very small numbers and need to be interpreted with great caution. We have sought to establish why no leukaemia cases were recorded by the NIFS, whereas two cases of leukaemia and two cases of NHL were reported in the RLS. Given that the RLS included work forces not included in the NIFS there was in principle the possibility that a subgroup of female workers in the RLS population might have a real and significant risk associated with their employment. However, we have been informed by the RLS authors that the mothers of the four LNHL cases in the study worked at three different sites.

6.37 The small number of cases of childhood cancer in the studies of the offspring of female radiation workers described above results in substantial statistical uncertainties. Consequently, we cannot be sure whether or not there is a genuine excess of childhood cancer among the offspring of female radiation workers. We are reassured by the fact that exposures of radiation workers have in general declined considerably since the 1970s. There is also now a restriction to 1 mSv for exposure of the abdomen of a woman after pregnancy has been declared. Nevertheless, it would be prudent to regard the processes that occur during pregnancy leading to childhood cancer (including particularly leukaemia) as being of continuing interest to radiation biologists and we are making recommendations to that effect.

CHAPTER 7

SUMMARY AND CONCLUSIONS

7.1 This report was written as part of the ongoing investigation into the cluster of cases of childhood leukaemia and cancer that occurred in Seascale, Cumbria, between 1954 and 1991. The purpose of this report is to review the evidence on whether there is an increased risk of childhood leukaemia and other cancers in the offspring of parents occupationally exposed to radiation before the conception of their children.

7.2 This report examines in detail one hypothesis that has been put forward to account for the Seascale cluster. Gardner et al (1990) suggested that damage to the germ cells of parents exposed to radiation before conception of their children increases the risk of childhood leukaemia and other cancers (the parental preconceptional irradiation, PPI effect). The report also refers to another hypothesis, proposed by Kinlen, and discussed in our Fourth Report. It suggests that the excess cases (of leukaemia in particular) reflect an abnormal reaction to a previously unencountered infection introduced through the large amount of migration into the area (population mixing).

Is there a PPI effect?

7.3 This report has examined evidence from experimental studies of the response of cells and of animals to radiation exposure. Induction of cancer in the offspring of irradiated parents (PPI) is regarded as possible in principle. However, where it has been examined in mice, it has not been found in all strains. In those strains where it has been reported the incidence is higher than can be explained by established mechanisms, but not so high that it could account for the Seascale cluster.

7.4 We have reviewed recent epidemiological studies of the offspring of radiation workers in the UK, the USA, and Germany, together with those reports available at the time of our Fourth Report. None of the studies has reported an increased rate of solid tumours in children. It is only the UK and German studies that suggest that the offspring of male radiation workers are about twice as likely to develop childhood leukaemia or non-Hodgkin's lymphoma (LNHL) as other children. The balance of the evidence indicates that this excess is in general not related to radiation dose. It is our opinion that it may be associated with lifestyle factors, or work practices or population mixing (although the biological mechanism of the population mixing effect is still not established). To put the figures into perspective we note that Gardner et al (1990) reported relative risks for LNHL of up to 3.2 for the children of men employed in various industries other than the nuclear industry and also relative risks below one.

7.5 The authors of the Record Linkage Study (RLS) concluded 'If there is any increased risk for the children of fathers who are radiation workers it is small in absolute terms. In Britain the average risk by age 15 years is 6.5 per 10,000; our best estimate is that the increase is 5.4 per 10,000'. We also note that the Nuclear Industry Family Study (NIFS) found a similar result for radiation workers while on the other hand did not detect any increase in the incidence of leukaemia or all cancers among children born of nuclear industry

employees as a whole (which included non radiation workers) since 1965 in comparison to the general population of England and Wales.

7.6 A number of epidemiological studies have failed to find evidence for a general PPI effect either among offspring of survivors of the atomic bombs in Japan or of workforces exposed to radiation. We find no convincing evidence to suggest that ionising radiation alone at the doses to which male nuclear industry radiation workers have been exposed, results in an increased incidence of childhood cancer. We also note that current levels of occupational exposure are low and are well below those experienced by workers more than 30 years ago. The number of cases of childhood cancer and leukaemia in the children of female radiation workers has been too small to draw conclusions about whether they are at greater risk than other children.

The Seascale cluster

7.7 The currently available evidence indicates that population mixing is responsible for a substantial part of the excess of LNHL among young people in Seascale. There is strong circumstantial evidence for the involvement of infectious agents in the population mixing effect, although the biological mechanism is not clear. Nevertheless, in contrast with the general situation, several studies of Sellafield employees have reported a significant association of leukaemia and non-Hodgkin's lymphoma with PPI. The most recent work in this area (the Cumbria study of Dickinson and Parker, 2002) is not independent of the original study of Gardner et al (1990) but includes three more cases and is of cohort rather than case–control design. The excess cases associated with paternal preconceptional exposure largely occurred between 1950 and 1970, were associated with high paternal doses, and lived predominantly in the village of Seascale and not in the more distant towns where the majority of radiation workers have lived. Gardner and the HSE study (HSE, 1993, 1994) found a steep and statistically significant increase in levels of LNHL with PPI dose in Seascale. Dickinson and Parker, using the same number of Seascale cases (6) but a different method of analysis, found a much less marked increase in LNHL with dose. However, these analyses are based on few cases and neither of the models used fit the data particularly well. Both the Dickinson and Parker study and the HSE study broadly support the association reported by Gardner et al, lowering to some extent the probability that the association is due to chance. It is possible that the apparent dose–response effect in Seascale is due to confounding between the level of dose and the level of some other factor such as population mixing. Put simply, the highest occupational exposures to fathers may have occurred at just those times when the population mixing effect in Seascale was at its greatest.

7.8 It remains possible that an undiscovered factor was operating in Seascale in the 1950s and 1960s that added to or perhaps interacted synergistically with a dose-related radiation effect that would otherwise have been too small to measure. We note the new evidence that in male germ cells of mice radiation damage can be extended to certain DNA sequences that have not themselves been subject to direct radiation damage and also to sequences in cells descended from the irradiated cells, essentially amplifying the effect of the initial radiation damage. This could, in principle, underlie the enhanced sensitivity of the offspring of irradiated mice to a carcinogenic chemical. It is not known whether the same mechanisms would work in people. An interaction between such changes and a specific Seascale factor is not impossible, although the strength of the interaction required would need to be very large. The obvious candidate for such a factor would be population mixing (presumed to be a surrogate for exposure to unknown infectious agents) which was extreme in and around Seascale for several decades. It would, however, be necessary to postulate an infectious agent (or other factor) that was unique or almost unique

to those radiation workers who lived in that village. We also emphasise that the mechanism of the amplification effect is unknown. Moreover, there is currently no direct evidence linking the amplification effect in germ cells to leukaemia in offspring. Until there is a better understanding of these mechanisms further speculation is unwarranted, but it is right that we note that such an interaction cannot be excluded at the present time.

7.9 The Seascale 'cluster' may not have a single explanation; one-third of the cases are of cancers other than LNHL, for which some relation to paternal radiation dose has been reported. We also note that leukaemias, for which a population mixing hypothesis was originally proposed, constitute less than half the cases. It is possible that more than one causal factor is responsible.

7.10 If there is an excess of cancers other than LNHL in children and young people in Seascale which arise for reasons other than chance then there is no clear indication of what these reasons might be. Some unrecognised factor may be responsible. For example, it is possible that infection relation related to population mixing might have a more general role than originally suggested (i.e. for childhood leukaemia), but evidence for this suggestion is lacking. The numbers of cases are small and this limits the conclusions that can be drawn.

CHAPTER 8

RECOMMENDATIONS

Recommendation 1 Some radiation-induced changes in the genome in repeat DNA sequences, have been observed experimentally to occur in germ cells of male mice at frequencies higher than hitherto suspected, implying that some regions of the genome may be more susceptible to ionising radiation. We recommend that experiments be undertaken to elucidate the underlying mechanisms behind these observations. This will aid in establishing what, if any, effect such changes may have on current estimates of risk associated with radiation exposure.

Recommendation 2 Currently, there is little understanding of how mutations in certain repeat DNA sequences might affect human health. We recommend that basic research in this area should be encouraged.

Recommendation 3 We are aware of recent work which has shown that the initiating event for certain subtypes of childhood leukaemia occurs during pregnancy and this may be linked to the subsequent development of leukaemia in that child. Further research in this area is under way and we recommend that the appropriate authorities ensure that sufficient funds are available so that this research might continue and, if necessary, expand.

Recommendation 4 We reiterate Recommendation 4 of our Fourth Report, that was concerned with the need for basic research into interactions between radiation and other agents. We also reiterate Recommendation 5 of our Fourth Report in which we stated that our inability to identify causative mechanisms to explain all the leukaemia and non-Hodgkin's lymphoma excesses identified in some areas of Great Britain reflects the present inadequate state of knowledge regarding the causes of childhood leukaemia. It is possible that such excesses will continue to elude explanation until underlying mechanisms are better understood. We expect such understanding to come from current and future initiatives in leukaemia and cancer research, whether related to radiation or not.

Recommendation 5 The high-grade epidemiological studies reviewed in this report were all dependent on access to data held by a number of British cancer registries. procedures concerning the future use of such data are being reviewed. We recommend that Government examines any proposed changes in detail so as to ensure that similar epidemiological studies will not be compromised in the future.

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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.

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
(sometimes spelt anemia) is 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.

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.

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.

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.

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).

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 like 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.

HODGKIN'S DISEASE
A form of malignant lymphoma that is characterised by painless enlargment of lymphatic tissue and the spleen and often involves symptoms such as fever, wasting weight loss, anemia, 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.

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.

INTRAPERITONEAL
Into the cavity surrounding the intestines, bladder, ovaries, etc.

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.

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.

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, 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.

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)
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.

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.

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.

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.

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 measure of the probability of a (generally) unfavourable outcome. *(See* ***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 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, Cumbria).

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.

TELOMERE-LIKE ARRAY
s*ee 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 p-VALUE*

URANIUM (U)
A hard grey metal which exists in seven isotopic forms (uraniuim-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 daughter 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 usually emitted by an X-ray machine or an excited atom.

APPENDIX B

COMMITTEE ON MEDICAL ASPECTS OF RADIATION IN THE ENVIRONMENT

CHAIRMAN

Professor B A Bridges OBE BSc PhD CBiol FIBiol
MRC Cell Mutation Unit
University of Sussex
Brighton

PRESENT MEMBERS

Professor Freda Alexander BA MSc PhD
Department of Community Health Services
University of Edinburgh *(from April 2000)*

Dr T Atkinson BSc PhD
Department of Geological Sciences
University College London *(from April 2000)*

Professor R A Cartwright BA MB BChir MA PhD FFOM FFPHM
Leukaemia Research Fund Centre for Epidemiology
University of Leeds

Professor Sue Cox BS MPU MIOSH FRSH
Director of the Business School
Loughborough University

Dr G J Draper OBE MA DPhil Hon MFPHM
Childhood Cancer Research Group
University of Oxford

Professor O B Eden MBBS D(Obst)RCOG MRCP(UK) FRCP (Edin) FRCP FRCPath FRCPCH
Academic Unit of Paediatric Oncology
Christie Hospital NHS Trust
Manchester

Professor A T Elliott BA PhD DSc CPhys FinstP FIPEM
Western Infirmary, Glasgow *(from April 2000)*

Professor Neva Haites BSc PhD MBChB MRCPath
Department of Medical Genetics
Aberdeen Royal Hospital NHS Trust

Professor J Little BA MA PhD
Department of Medicine and Therapeutics
University of Aberdeen

Professor T J McMillan BSc PhD
Institute of Environmental and Natural Sciences
Lancaster University

Dr Louise Parker BSc PhD
Sir James Spence Institute of Child Health
Newcastle University *(from April 2000)*

Dr Margaret Spittle MSc MB BS MRCS FRCP FRCR DMRT AKC
Meyerstein Institute of Radiotherapy and Oncology
Middlesex Hospital

Professor A M R Taylor BSc MSc PhD
Department of Cancer Studies
University of Birmingham

Professor J Thacker BSc PhD
MRC Radiation and Genome Stability Unit
Oxfordshire

Professor R Waters BSc PhD
School of Biological Sciences
University of Wales, Swansea

Professor J M A Whitehouse MA MD FRCP FRCP (Edin) FRCR
Imperial College School of Medicine
University of London

Professor E Wright HNC BSc PhD CBiol MIBiol MRCPath FRCPath
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University of Dundee

FORMER MEMBERS WHO SERVED DURING THE PREPARATION OF THIS REPORT

Professor K Boddy OBE CBE BSc MSc PhD CPhys FInstP DSc FRSE
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Newcastle General Hospital *(until March 2000)*

Professor K K Cheng BSc MB BS PhD MFPHM MRCGP FHKCCM FHKAM
Department of Public Health and Epidemiology
University of Birmingham *(until March 2000)*

Professor K M Clayton CBE MSc PhD HonDSc
Formerly of School of Environmental Sciences
University of East Anglia, Norwich *(until March 2000)*

Professor Sarah Darby BSc MSc PhD
Clinical Trial Service Unit
University of Oxford *(until March 2000)*

SECRETARIAT

Dr R Hamlet BSc PhD Cbiol MIBiol (Scientific)

Dr J R Cooper BSc DPhil (Scientific)

Dr C Sharp MSc FRCP MRCGP MFOM DCH DAvMed (Medical) *(until March 1999)*

Dr Jill Meara MA MSc BMBCh FFPHM (Medical) *(from September 2000)*

Dr G M Kendall BSc MSc PhD FRSC CChem FInstP CPhys FRSE (Scientific) *(from June 1999)*

Dr Carol Attwood BSc PhD (Minutes) *(until September 1999)*

Dr M Little BA DPhil FRSS (Minutes) *(September 1999 until February 2000)*

Mrs Alison Jones (Minutes) *(March 2000 until September 2000)*

Miss Jane Bradley MRSC CChem (Minutes) *(from December 2000)*

Dr Nezahat Hunter BSc PhD *(from March 2000)*

Miss Julie Kedward (Administrative)

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

Environment Agency

Food Standards Agency

Health and Safety Executive

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

Medical Research Council

Ministry of Defence

National Radiological Protection Board

Office for National Statistics

Scottish Environment Protection Agency

Scottish Executive

Welsh Assembly Government

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
Dr L Parker
Professor A M R Taylor
Professor J Thacker
Professor J M A Whitehouse
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 M 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)*
Health and Safety Executive

Mr G Hooker
Department of Health

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, shareholding, 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 para 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 – 2001

Member	Company	Personal interest	Company	Non-personal interest
Prof F Alexander		None		None
Dr T Atkinson		None	UKAEA	Consultancy
Prof B Bridges		None		None
Prof R Cartwright		None		None
Prof S Cox		None	BNFL	MSc students and short-course attendees
Dr G Draper		None		None
Prof O Eden		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
Dr L Parker		None	Westlakes Research Inst	Research project funding
Prof T McMillan		None	Westlakes Research Inst	PhD students and consumables
Dr M Spittle		None		None
Prof A M R Taylor		None		None
Prof J Thacker		None		None
Prof R Waters		None		None
Prof M Whitehouse		None		None
Prof E Wright		None		None