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

FOURTEENTH REPORT

Further consideration of the incidence of childhood leukaemia around nuclear power plants in Great Britain.

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Committee on Medical Aspects of Radiation in the Environment

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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).The terms of reference for COMARE are:

> 'to assess and advise Government and the devolved authorities on the health effects of natural and man-made radiation and to assess the adequacy of the available data and the need for further research'

ii In 25 years of providing advice to Government and the devolved authorities COMARE has to date published 13 major reports (see Appendix E), in addition to numerous other statements and documents, mainly related to exposure to naturally occurring radionuclides, such as radon and its progeny, or to man-made radiation, usually emitted by major nuclear installations.

iii In 2009, the Department of Health asked COMARE to conduct a review of recent publications on the incidence of childhood leukaemia in the vicinity of nuclear power plants, in relation to the conclusions in the tenth and eleventh COMARE reports (COMARE, 2005, 2006). This work was prompted in part by the publication of a German report on the same subject known as the *Kinderkrebs in der Umgebung von Kernkraftwerken* (KiKK) study (Kaatsch et al, 2008a; Spix et al, 2008). To achieve this, COMARE set up a subgroup of committee members and external experts to conduct this work, the KiKK Review Subgroup. When the Subgroup had finished its review, the report was presented to COMARE for consideration by the full committee, with the aim that the information would be presented to the Department of Health in due course. That information is contained in this, our fourteenth report.

iv COMARE previously considered the incidence of childhood cancer in the vicinity of nuclear power plants between 1969 and 1993 and concluded that 'there is no evidence from this very large study that living within 25 km of a nuclear generating site in Britain is associated with an increased risk of childhood cancer' (COMARE, 2005). The aim of this COMARE report has been to provide further information for the Department of Health on the incidence of childhood leukaemia in the vicinity of nuclear power plants in Great Britain in comparison with the situation in other countries and to determine whether there is any evidence to support a revision of the previous COMARE advice. However, the interest in this issue extends beyond the remit of the Department of Health and the recommendations made in this report will be pertinent to other government departments and agencies, particularly with the consideration of a new nuclear build programme.

CHAPTER 1

INTRODUCTION

1.1 The aim of this report is to undertake a further review of the incidence of childhood leukaemia in the vicinity of nuclear power plants (NPPs) in Great Britain, with particular reference to recent publications, including the German *Kinderkrebs in der Umgebung von Kernkraftwerken (KiKK)* study and studies from other countries (eg France and Finland), and in relation to the conclusions in the tenth and eleventh COMARE reports (COMARE, 2005, 2006). This review considers Great Britain (England, Scotland and Wales) and not the UK, since no NPPs are present in Northern Ireland.

1.2 In this report, COMARE presents a new geographical data analysis on the incidence of leukaemia in children under 5 years of age, living in the vicinity of NPPs, using cancer registration data currently available for Great Britain. The report has also characterised the pathology of the cases of childhood leukaemia and non-Hodgkin lymphoma (NHL) living near NPPs and compared them with matched cases from individuals not resident near NPPs. The report investigates additional factors, which have not been considered in previous COMARE reports and which may contribute to variation in the results from different countries. It describes the cancer registries of several countries in Europe. It also describes the types of reactor present in selected European countries, considers the radioactive discharges from the NPPs of these countries and the consequent assessed radiation doses to the general population.

1.3 The report of the Independent Advisory Group chaired by Sir Douglas Black (Black, 1984) concluded that there was a raised incidence of leukaemia in young people living in the village of Seascale, adjacent to the Sellafield nuclear site in northern England. Since the publication of this report, numerous studies and reports on the possible risks of childhood leukaemia in the vicinity of nuclear sites have been published. Some studies have observed positive associations between the risk of childhood leukaemia and proximity to a nuclear site, but only a few of these have been statistically significant and no conclusive evidence has been obtained to determine whether living near a nuclear installation might be a cause of childhood leukaemia. Previous detailed critical reviews by COMARE and others have concluded that the radiation doses arising from the operation of nuclear installations are not nearly high enough to cause increases in childhood leukaemia (COMARE, 1988, 1989, 1996). There is growing epidemiological evidence that childhood leukaemia is linked to infections; two major hypotheses are that childhood leukaemia is either a rare response to a specific common infection (Kinlen, 2011) or a rare response to general exposure to infectious agents that is enhanced by delayed exposure (Greaves, 2006). However, the biological mechanisms underlying these hypotheses remain the subject of considerable scientific debate.

1.4 Concern has arisen again following the recent publication of an epidemiological study in Germany. This study, entitled the *Kinderkrebs in der Umgebung von Kernkraftwerken (KiKK)* study, reported a statistically significantly increased risk of leukaemia among children aged less than 5 years

living within 5 kilometres of NPPs (Kaatsch et al, 2008a; Spix et al, 2008). In contrast, our tenth report (COMARE, 2005) found no evidence of excess leukaemia incidence at ages 0–14 years within a 25 km area around any of the NPPs in Great Britain, nor was there any evidence of a tendency for childhood leukaemia rates to be higher nearer to these sites. A further analysis using the data considered in our tenth report found no statistically significantly raised risk for childhood acute leukaemia within 5 km of British NPPs for children under 5 years of age (Bithell et al, 2008, 2010). These findings for Great Britain are consistent with results from the studies conducted in France and Finland, which also found no statistically significantly raised risk of leukaemia in children under the age of 5 years around NPPs (Evrard et al, 2006; Heinavaara et al, 2010; Laurier et al, 2008a,b), although the authors acknowledged that the small sample sizes limited the strength of the conclusions.

1.5 Our tenth report (COMARE, 2005) concluded that the situation for the other nuclear sites (facilities with a primary function that is not power generation) is more complicated. The analyses in that report confirmed previous COMARE findings of excess childhood leukaemia and NHL incidence around Sellafield, Dounreay and Burghfield. Historically, Sellafield is the nuclear site in the UK with the largest radioactive discharges. Our fourth report (COMARE, 1996), which focused on Sellafield and childhood leukaemia in Seascale, concluded that 'on current knowledge, environmental radiation exposure from authorised or unplanned releases could not account for the excess' [of leukaemia and NHL]. COMARE has established a subgroup to specifically review the incidence of childhood leukaemia and other cancers in the vicinity of Sellafield and of Dounreay up to the present time, in accordance with recommendation 5 of the eleventh report (COMARE, 2006).

1.6 In the eleventh report, COMARE examined the general pattern of childhood leukaemia and other childhood cancers in Great Britain and concluded that many types of childhood cancers 'have been shown not to occur in a random fashion'. The incidence rates in different geographical and social circumstances differ more than would be expected from simple random or chance variations. This uneven distribution (or clustering) occurs at all levels of population distribution throughout the country, down to local levels, such as electoral wards (COMARE, 2006).

1.7 Previous case–control studies and geographical studies in different countries have investigated possible associations between residence in the vicinity of NPPs and the risk of childhood cancer. Although many of these studies are believed to be relatively free of confounding or bias, caution should be employed when making inferences about childhood cancers near NPPs. There are important statistical limitations within some of the studies, eg if the number of children in the study is small, then the study will have low power to detect and estimate raised cancer risk. Furthermore, there are other potential uncertainties arising from confounding and sources of bias in some studies. If confounding factors are not measured or considered, distortion may result. For example, the socioeconomic and lifestyle factors of individuals may confound a relationship between the area of residence near NPPs and childhood cancer. There are also differences in epidemiological study designs between studies.

1.8 Childhood leukaemia is a rare disease, affecting approximately 500 children (0–14 years of age) every year in the UK*. Therefore, sample numbers in individual epidemiological studies are frequently small. Indeed, the KiKK study included only 37 cases of leukaemia in children under 5 years of

* http://www.leukaemia.org/about-leukaemia/incidence-of-childhood-leukaemia (accessed December 2010).

age, living within 5 km of an NPP over the 23 year period of the study and the new analysis for Great Britain presented in this report observed 20 cases (under 5 years of age, living within 5 km of an NPP) over the 35 years of the study.

1.9 COMARE has been in contact with the investigators of the KiKK study regarding matters of fact relating to the study and is very grateful for the help and support provided and for the prompt nature of the responses. It should be recognised that the interpretation and conclusions given in Chapter 4 of this report are and remain solely the views of COMARE.

CHAPTER 2

EPIDEMIOLOGICAL STUDIES: GEOGRAPHICAL AND CASE–CONTROL STUDY DESIGNS

Introduction

2.1 Epidemiological studies considered in this report are of a kind known as *observational,* ie they involve making observations on individuals or populations without any possibility of controlling the factors involved. This is in contrast to *experimental* designs, such as are used, for example, in agricultural or clinical trials. Observational studies attempt to infer causes of a disease, *D*, for example, by looking for its association with possible explanatory factors. This association may loosely be termed *correlation*, although this term has a rather precise meaning and so is not always appropriate. Such an association, however, does not imply a causal relationship. It is a symmetrical relationship and unable by itself to indicate the direction of causation between two variables. More significantly, both a disease, *D*, and a given factor, *F*, may be associated with a third factor, *C*, which gives the appearance of an association between *D* and *F*. This is the phenomenon known as confounding and *C* is known a *confounder*. There are ways of allowing or controlling for confounding, but only provided relevant confounding variables have been measured. In analyses, it is never possible to be sure that the effects of all possible confounders have been eliminated. This is a fundamental limitation of all observational studies and it means that the conclusions must inevitably be less certain than those from experimental evidence. Nevertheless, epidemiological observations have proved extremely useful in many areas of medicine, either because they suggest lines of enquiry that can be pursued by other means, or because they can complement our knowledge from other sources.

Epidemiological study designs

2.2 The simplest kind of epidemiological observation study typically observes the occurrence of death or disease in individuals who differ in measurable ways. Very often, though not always, groups of similar individuals are identified and followed up to see which suffer from a particular disease at some time in the future. For this reason, studies of this kind are quite generally known as *cohort studies.* The essential feature is the consideration of one or more explanatory factors as fixed and the disease as a subsequent response using probabilistic models.

2.3 An alternative to the cohort design is obtained by starting with fixed groups with and without the disease – known as cases and controls – and observing their characteristics. In this *case–control study* approach, the case and control groups are fixed and the observed factors, *F*, are modelled as if they were random. Of course, this does not claim that the attributes *F* are caused by disease *D*, and indeed *F* will almost always be regarded as a precursor to *D*. But the occurrence of a particular value of *F* can be regarded as a random response if it is assumed that cases and controls are sampled randomly from a hypothetical pool of all possible individuals.

2.4 Cohort and case–control studies have their own advantages and disadvantages. Cohort studies generally require the collection of information on large groups of individuals, many of whom will be unaffected by *D*. They

consequently tend to be very expensive and to yield relatively little information, especially for investigations of rare diseases. Sometimes, however, information on existing cohorts can be exploited and, in this case, the cost is much lower. Case–control studies appear to provide a more efficient way of obtaining information and they can provide straightforward access to details for the individuals that can be used to adjust for a possible confounding effect. They are, however, subject to a number of possible sources of bias and they are also unable to calculate actual disease rates since they lack the population denominators needed. This matters much less than might appear since it is possible to calculate the *odds ratio* (OR) – ie the ratio of the odds on getting the disease in the exposed and unexposed groups. This is a useful measure in its own right, but it also turns out that, for fairly rare diseases, it is very close to the *relative risk* (RR) or ratio of absolute risks of disease in the two groups. More detailed aspects of case–control study design are discussed below.

2.5 Within these two broad groups, there are many more specific designs exploiting particular epidemiological situations. One of these is the *geographical study* and most of the analyses considered in this report are of this kind. In essence, groups of individuals are defined by their areas of residence and attributes of these areas are used as the explanatory factors, *F*. Within each area the numbers of individuals suffering from disease *D* are recorded and related to the size of the group. The response is the occurrence of *D* and this makes this analysis a type of cohort study. Thus, for the analysis described in Chapter 6, for example, the areas of residence are the electoral wards (or equivalent areal units) in Britain; the response variable is the *standardised incidence ratio* (SIR) for childhood leukaemia, ie the number of children diagnosed with the disease in each area in a defined time period divided by an estimate of the average number of children at risk. Factors of interest include the distance of the area from the nearest NPP and other attributes of the area that may be confounders, such as the (average) socioeconomic status in the area. As far as the individuals are concerned, the common value for an area is imputed to all the individuals in it and such a study is sometimes termed an 'ecological study'. For this reason, analyses of areas on this basis are sometimes said to be subject to the 'ecological fallacy' or 'ecological bias'. The latter refers to the fact that relationships are attenuated by considering them at the areal rather than the individual level, ie estimates of risk are biased downwards. The power of tests to detect an effect is also reduced, but such tests are still valid and in this sense the term 'fallacy' is misleading. Such studies are known by various other names, such as 'areal', 'group' or 'aggregate', each reflecting one particular aspect of the study design. The term 'geographical' is used here for continuity with previous COMARE reports, but the reader should be aware that the case–control study considered in Chapter 4 – the KiKK study – also has a geographical element.

Geographical studies

2.6 In spite of the limitations described above, geographical studies remain a popular study design among epidemiologists for several reasons. They generally employ data that are already available in the form of local and national registers. This means that a study can be carried out relatively quickly and cheaply; the relatively large amount of information available leads to more power for a study and this helps to offset the loss of power through the attenuation mentioned above. The available data will generally be in areas constructed for some political or administrative purpose and these may not be ideal for an epidemiological investigation, although the fact that they reflect the population distribution and demographic differences is often very helpful. Such areas are usually available in a hierarchical form – in England, for example, in census enumeration districts within electoral wards in county districts within counties and regions – and the choice of areal unit may be important. Smaller units permit a more precise focus on geographical features of interest, but

generally have less good information available from censuses etc. The smaller numbers in them may also pose problems for some kinds of statistical presentation or analysis because of the large sampling errors, although this is less of a problem now owing to the availability of more sophisticated methods of analysis.

2.7 A major difficulty in the UK is the determination of the population size in a given area. Household migrations from one address to another are quite substantial and – although they tend to cancel one another out – there are also significant redistributions of the population as industries change and migrants enter and leave the country. Inevitably, therefore, the decennial census provides only an approximate value for the average population in any area and this inevitably leads to inaccuracy in estimates of the SIRs, for example. Nevertheless, for the study of a risk unrelated to population movements, the bias resulting from this limitation may reasonably be expected to be of secondary importance.

Case–control studies

2.8 In a case–control study, the number of cases will be determined by the availability of the data and the resources available; it is not necessary that all the cases in a given region or period should be considered, although it is certainly important to ensure that the selection of cases is not affected by anything related to the factors under investigation. The comparison with the controls involves errors from the randomness of the responses in both the cases and the controls and, for this reason, it is often convenient and beneficial to reduce the error associated with the controls by choosing more controls than cases.

2.9 The controls should be chosen to be as fully representative as possible of the population at risk of disease *D*, from which the cases are drawn. They should be free of *D* throughout the observation period during which the population at risk gave rise to the cases, and they should have (potentially) remained under observation throughout that time period. They are 'allowed' to become cases of *D* subsequently, but not within the observation period during which the cases under study were identified. The problem of dealing with the effects of confounding factors for which information is available for both cases and controls may be dealt with either by using appropriate multivariate methods for the analysis of risk, or by stratification or by matching of the controls to the cases. The last can be achieved either by choosing the group of controls to have similar properties to the group of cases (known as group matching) or by choosing one or more controls to be similar to each individual case (individual matching). This can be used as an effective way of eliminating potential confounding variables, but it has disadvantages. It makes it impossible to examine the effect of the matching factors on *D* itself and it is generally regarded as better to allow for differences due to different variables at the analysis stage. The precept that controls should be similar to the cases also means that both groups may be atypical of the population as a whole, so that the inferences made are less easily generalised. Nevertheless, it is crucially important that cases and controls come from similar sources wherever possible. Information from essentially different sources may incorporate unknown but subtle differences. They should also be treated similarly, being handled as far as possible by procedures that conceal the distinction between the cases and controls. How this is achieved depends very much on the context of the study and it is hard to generalise.

2.10 Subtle differences in the way that cases and controls are selected may lead to what is known as *selection bias*. For example, if responsibility for registering cases lies with someone who is doubtful about the inclusion and knows the object of the study and the exposure status of the subject, it could influence the results, often to an unexpected extent. Any application of subjective

judgement is dangerous from this point of view, of course. So too is reliance upon memory in interviews with subjects or their families, since this can easily lead to an important *recall bias* between cases and controls. What biases actually occur depends on the context and the design of the investigation. Numerous books on epidemiology address these issues in detail. For example, the paper by Sackett (1979) identifies as many as 35 different biases that can occur with case–control studies.

2.11 Most of the general advantages and disadvantages of case–control studies apply to those concerned with geographical location. It is relatively easy to locate a subject's address, but comparison with controls or with the population at large is generally difficult. Population registers are notoriously difficult to keep up to date and, even if it is sometimes available, a register of the whole population may be atypical of the cases observed with *D* in some significant respect. The safest comparison is often to be made with individuals from the same source as the cases but experiencing some disease other than *D*. A common example is the use of *hospital controls*. Clearly, the comparison is not quite what we would choose experimentally, but it is often more reliable than anything else available.

Summary

2.12 Epidemiological investigations are essentially observational and accordingly suffer from the problem of confounding, or the influence of other – possibly unobserved – factors. Study designs fall into two broad groups, although there are many variations designed to exploit different situations. The two commonly used for geographical investigations are the geographical study and the case–control study. In the former, SIRs are computed in different small areas whose geographical and demographic characteristics are imputed to the individuals in them. In the latter, geographical and other characteristics of cases with a disease are compared with unaffected controls in order to estimate the ORs of one or more factors. Both kinds of study have strengths and weaknesses, which depend substantially on the details of the design and the area of application.

CHAPTER 3

REVIEW OF STUDIES ON THE RISK OF LEUKAEMIA IN YOUNG PEOPLE LIVING IN THE VICINITY OF NUCLEAR INSTALLATIONS IN GREAT BRITAIN AND OTHER COUNTRIES

Introduction

3.1 In this chapter, the epidemiological evidence in Great Britain and other countries (apart from Germany, which is considered separately in Chapter 4) concerning childhood leukaemia and nuclear installations is reviewed using both recent and earlier studies. The key features of the design and results of selected national studies relating to leukaemia incidence in children or young people for groups of nuclear installations are summarised in Table 3.1. Results for nuclear power plants (NPPs), in contrast to other nuclear installations, are highlighted in this review.

3.2 Interest in possible health effects among the general public living around nuclear installations due to low level radiation exposure developed in the early 1980s. Earlier studies were reviewed by Tokuhata and Smith (1981). The issue was brought into the public spotlight by a television report in 1983 of the excess of childhood leukaemia incidence in the coastal village of Seascale, adjacent to the Sellafield nuclear installation, which was the subject of investigation by the Independent Advisory Group (Black, 1984) and the first COMARE report (COMARE, 1986). Further reports of excess cases of childhood leukaemia in the vicinity of nuclear installations followed, notably the raised incidence around Dounreay in northern Scotland and near Aldermaston and Burghfield in Berkshire, which were the subject of the second and third COMARE reports (COMARE, 1988, 1989), respectively. Here, attention will be concentrated upon studies of groups of nuclear installations, in particular NPPs, rather than individual nuclear sites.

Great Britain

Cancer mortality in small areas around nuclear facilities in England and Wales (Baron, 1984) (geographical study)

3.3 The first systematic review of the risk of cancer around nuclear installations in Great Britain was conducted by Baron (1984), who examined cancer mortality rates in pre-1974 local authority areas (LAAs) having more than half their area lying within 5 miles of 15 major nuclear installations in England and Wales for the periods before and after start-up of the installations, and the trends in standardised mortality ratios (SMRs) after start-up. For NPPs, small numbers prevented SMR trend analyses for childhood cancers, but SMRs were compared between an 'early period' (1963–1970) and a 'late period' (1972–1979). No consistent pattern of childhood leukaemia mortality was found, although the comparison was based on small numbers of deaths.

Cancer near nuclear installations (Cook-Mozaffari et al, 1987; Forman et al, 1987) (geographical study)

3.4 Cook-Mozaffari et al (1987) extended the work of Baron (1984), and the detailed findings were summarised by Forman et al (1987). Cancer mortality and incidence during 1959–1980 were examined in pre-1974 LAAs with at least

one-third of their population living within 10 miles of 15 major nuclear installations in England and Wales, and four distance zones of LAAs were constructed. Matched control LAAs situated away from installations were also used, and Forman et al (1987) used a relative risk (RR) estimate generated from the ratio of the SMRs for installation and control LAAs, to which they attached most weight. Concerns over incomplete cancer registration data for the areas and periods covered led Forman et al to concentrate upon cancer mortality rather than incidence. For the grouping of NPPs, the leukaemia mortality RR for the 0–24 year age group was non-significantly raised for all distance zones combined (RR = 1.13, 95% confidence interval (CI) = 0.83–1.55), while the association of RR with distance zone was marginally significantly negative (P = 0.054).

Geographical variation in mortality from leukaemia and other cancers in England and Wales in relation to proximity to nuclear installations, 1969–78 (Cook-Mozaffari et al, 1989a) (geographical study)

3.5 Arising partly from concerns over the control areas used by Cook-Mozaffari et al (1987) and Forman et al (1987), in 1989 the same group adopted an alternative approach to examine cancer mortality in post-1974 county districts (CDs) within 10 miles of a major nuclear installation. Cook-Mozaffari et al (1989a) conducted a log-linear regression analysis using data from all 402 CDs in England and Wales to adjust mortality RRs to account for social class, rural status, population size and health authority region. Three distance zones were also considered. For NPPs, the unadjusted leukaemia RR for the 0–24 year age group was 1.08 (95% CI = 0.92–1.25), while the adjusted RR was 1.15 (95% CI = 0.97–1.36); no trend with distance was found. A highly significant trend of the RR of leukaemia mortality in the 0–24 year age group (due to lymphatic leukaemia) with increasing socioeconomic status was found, although the degree of variation in the RR of leukaemia in young people was greater than would be expected by chance after adjusting for the four factors incorporated in the regression analysis.

3.6 In an extension of this study, Cook-Mozaffari et al (1989b) conducted the same analysis for CDs within 10 miles of eight potential sites of NPPs at which NPPs were planned but not built (or not operational during 1969–1978). Cancer mortality rates for CDs near potential sites were ‘strikingly similar’ to those for CDs near existing sites, which the authors interpreted as being due to the presence of some important unrecognised risk factors around both existing and potential sites.

Incidence of leukaemia in young persons in west of Scotland (Heasman et al, 1984) (geographical study)

3.7 Heasman et al (1984) examined leukaemia incidence during 1968–1981 among young people (0–24 years of age) living in postcode sectors lying within 10 miles of the two NPPs in Scotland that were operational at that time (Chapelcross and Hunterston). The observed and expected numbers of cases for Chapelcross were ‘very close’, while a 50% excess of cases around Hunterston was marginally significant at the 0.05 level.

Distribution of childhood leukaemias and non-Hodgkin’s lymphomas near nuclear installations in England and Wales (Bithell et al, 1994) (geographical study)

3.8 Using incidence data from the National Registry of Childhood Tumours, Bithell et al (1994) examined the association between leukaemia and non-Hodgkin lymphoma (collectively referred to as LNHL) diagnosed in the period

Table 3.1 Summary of selected national geographical studies investigating leukaemia incidence in children living near nuclear installations, in which groups of major nuclear installations, including groups of NPPs, have been considered

Country, period of study	Exposed areas	Control areas, matching or stratification variables	Outcome, age group (years)	Exposure group	Number of cases	Obs/Exp (SIR)	Source
England and Wales, 1966–1987	Electoral wards within 25 km of 23 nuclear installations and 6 potential sites	Expected numbers from national rates	LNHL, 0–14	8 NPPs	480	0.98	Bithell et al, 1994
				7 other major installations that emitted non-negligible quantities of radioactivity during the study period	1269	1.00	
				8 installations excluded from the two groups above either because emissions were believed to be small or because operations started too late to affect most of the children in study	1945	0.99	
				6 control sites that had been investigated for suitability, but never used	406	1.02	
Scotland, 1968–1993	Enumeration districts within 25 km of 7 nuclear installations	Expected numbers from national rates	LNHL, 0–14	3 NPPs	66	0.90	Sharp et al, 1996
				3 nuclear submarine bases	324	0.97	
				1 nuclear reprocessing plant	9	1.99	
England, Wales and Scotland, 1969–1993	Electoral wards within 25 km of 28 nuclear installations	Expected numbers from national rates	LNHL, 0–14	13 NPPs	692	0.96	COMARE, 2005
				15 other nuclear installations	2494	1.01	
			ML, 0–4	9 NPPs <25 km	50	Listed individually in the tenth COMARE report	
				4 NPPs <10 km	8		
				14 other nuclear installations <25 km	162		
				11 other nuclear installations <10 km	30		
England, Wales and Scotland, 1969–1993	Electoral wards within 5, 10, 25 and 50 km of NPPs	Expected numbers from national rates	Acute leukaemia, 0–4	13 NPPs	<5 km = 20 <10 km = 60 <25 km = 409	1.36 0.90 0.97	Bithell et al, 2008, 2010

Country, period of study	Exposed areas	Control areas, matching or stratification variables	Outcome, age group (years)	Exposure group	Number of cases	Obs/Exp (SIR)	Source
France, 1990–1998	'*Communes*' within 20 km of 29 nuclear installations	Expected numbers from national rates	Acute leukaemia, 0–14	19 NPPs	125	0.91	White-Koning et al, 2004
				29 installations (19 NPPs + 8 other sites, where 3 research installations are treated as a single site)	670	0.92	
			Acute leukaemia, 0–4	19 NPPs	<20 km = 114 <5 km = 5	1.05 0.96	Laurier et al, 2008a
France, 1990–2001	'*Communes*' within 40 km^2 areas centred on 24 nuclear installations based on assessed radiation dose	Expected numbers from national rates	Acute leukaemia, 0–14	18 NPPs	242	0.96	Evrard et al, 2006
				23 sites (18 NPPs + 5 others)	750	0.94	
			Acute leukaemia, 0–4	23 sites (18 NPPs + 5 others)	394	0.95	
Finland, 1975–2004 (analysis from start of operation – 1977 and 1979)	Municipalities within 15 km of NPPs	Expected numbers based on stratum-specific incidence for Finland	Leukaemia, 0–14	2 NPPs	16	1.01	Heinavaara et al, 2010

1966–1987 in children aged 0–14 years, and proximity of residence to 23 nuclear installations in England and Wales. Electoral wards with centroids lying within 25 km of 23 active installations and six potential sites were included in the study. Three groups of active installations were considered: (i) eight NPPs, (ii) seven other major installations that emitted non-negligible quantities of radioactivity during the study period, and (iii) eight installations excluded from the above groups either because emissions were believed to be small or operations started too late to affect most of the children in the study. In addition, the study considered six potential sites that had been investigated for suitability for an NPP, but where construction had not taken place and which were also included in the study of Cook-Mozaffari et al (1989b).

3.9 Standardised incidence ratios (SIRs) were calculated as the ratios of the observed numbers of cases to the expected numbers, the latter being obtained using a Poisson regression model with adjustment for socioeconomic status variables. Proximity to an NPP was tested using the linear risk score (LRS) test, which was designed to be sensitive to excess incidence in close proximity to a putative source of risk. There was no significant evidence of an increase in the SIR of childhood LNHL within 25 km of any of the sites considered or of the group of eight NPPs. Of the 29 sites studied, three produced statistically significant results using the LRS test: Sellafield ($P = 0.00002$), which was entirely due to the previously known cases in Seascale, the minor installation at Burghfield ($P = 0.031$), and one of the control sites ($P = 0.020$). For no NPP, or the group of NPPs, was the LRS test significant.

Incidence of childhood leukaemia and non-Hodgkin's lymphoma in the vicinity of nuclear sites in Scotland, 1968–93 (Sharp et al, 1996) (geographical study)

3.10 Sharp et al (1996) investigated the incidence of LNHL diagnosed in children aged 0–14 years in the vicinity of all seven major nuclear sites in Scotland during the period 1968–1993. Three of the seven installations were NPPs, three were nuclear submarine bases, and the other installation was the fast reactor and nuclear fuel reprocessing site at Dounreay. Areas composed of enumeration districts with centroids within a 25 km radius of an installation were investigated. The LNHL data were verified from multiple sources and a diagnostic review was carried out for all but a small proportion of cases, whether resident near nuclear sites or elsewhere. There was no significantly increased SIR for LNHL in the 25 km zone around any nuclear site in Scotland. There was a significant excess risk in the zone around Dounreay, with a P-value of 0.03, when applying Stone's maximum likelihood ratio test (Stone, 1988), which was only partly accounted for by the socio-demographic characteristics of the study area. The result of an LRS test for a trend of decreasing risk with increasing distance from the installation was not statistically significant for any site. For the three NPPs, no unusual finding was reported.

The incidence of childhood cancer around nuclear installations in Great Britain (COMARE, 2005) (geographical study)

3.11 The tenth COMARE report (COMARE, 2005) examined the incidence of LNHL and other cancers in children under the age of 15 years in the vicinity of the 28 major nuclear installations in England, Wales and Scotland during 1969–1993, using data from the National Registry of Childhood Tumours (NRCT), which comprised 12,415 cases of LNHL and 19,908 cases of other cancers. The 28 nuclear installations were divided into two groups: (i) 13 NPPs (see Figure 3.1) and (ii) a heterogeneous group of 15 other nuclear installations used for research, commercial and military purposes. The observed numbers of

cases were tabulated for each of 10,428 electoral wards or equivalent areal units; expected numbers were then calculated by Poisson regression modelling to adjust for region and socioeconomic status variables, using the methodology described by Bithell et al (1995). This adjustment serves the same purpose as standardisation, ie it allows for factors that are known or believed to affect the risk in the vicinity of the NPP or in individual wards.

3.12 The analyses conducted for our tenth report compared the observed numbers of cases in wards within 25 km of a nuclear site with the corresponding expected numbers; the ratios of observed to expected numbers (SIRs) were reported separately for each site. In addition, a non-parametric statistical test was used to assess the proximity of the cases to each individual installation within a 25 km circle. The test used was chosen separately for each site since the test characteristics generally depend on the population distribution. Five possible tests were considered in each instance and the one chosen was that which maximised the power to detect an effect of distance averaged over a number of different risk relationships. [More details of these tests and their application are given in our tenth report (COMARE, 2005).] Of the five tests, the most powerful one for the majority of sites was an LRS test based on the square root of the distance rank. The tests were carried out unconditionally and consequently were sensitive to both an overall excess in the area and a tendency for the risk to be larger nearer the centre of the circle.

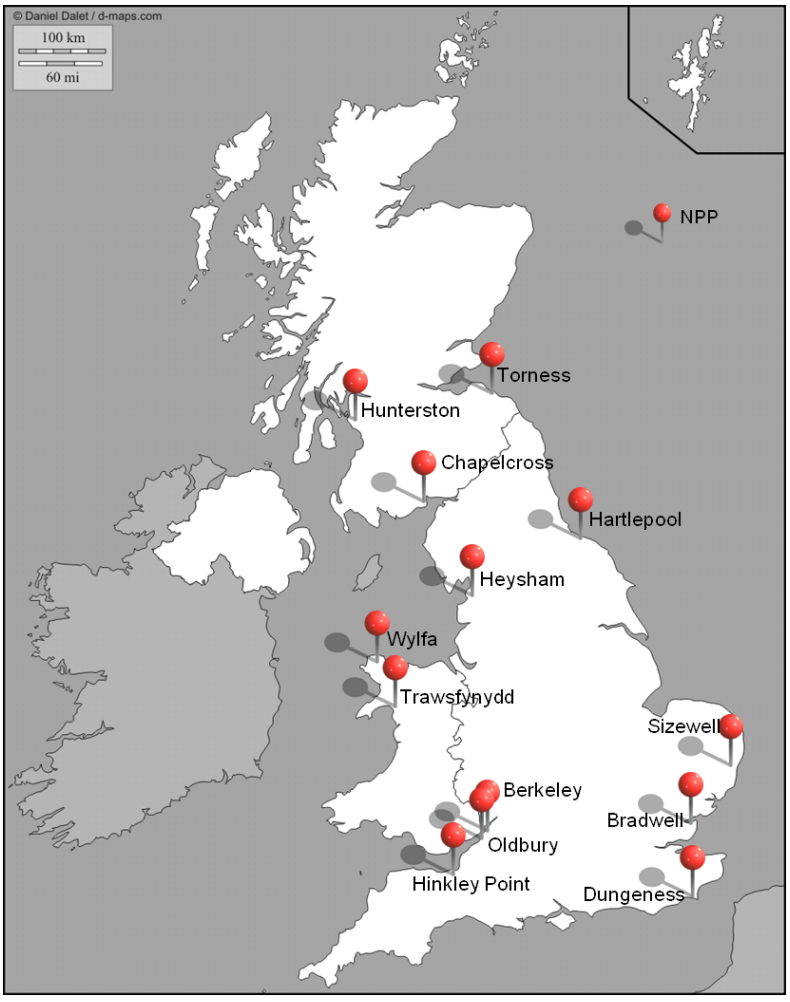

Figure 3.1 NPP sites in Great Britain

Map generated from image at D-maps.com (http://d-maps.com/m/royaumeuni/royaumeuni15.gif)

3.13 Our tenth report concluded that there was no significant evidence of excess numbers of cases of childhood LNHL or of other childhood cancers in any 25 km area local to the 13 NPPs (Bithell et al, 2008; COMARE, 2005). The report noted, however, that children living near some of the other nuclear sites showed significant excesses of LNHL: Sellafield, Dounreay and Burghfield, which had been extensively investigated in previous COMARE reports (COMARE, 1988, 1989, 1996), but also around the dockyard at Rosyth, which had not been reported previously. The results for Rosyth differed from those produced by Sharp et al (1996) in that they showed evidence of a trend in LNHL risk with distance from the site. Our tenth report concluded that this difference was due to the distribution of the cases around the site; the variation between the two studies is small in numerical terms and may be explained by technical differences.

3.14 Our tenth report also examined the incidence of myeloid leukaemia (ML) among children aged 0–4 years living within 10 and 25 km of nine NPPs and 14 other nuclear sites in 1969–1993 in response to a study (Busby et al, 2001), which found an excess of cases in Wales 10 km away from Oldbury NPP for the period 1974–1990. The analysis in the tenth report showed a slight tendency for ML cases to live near the NPP at Hartlepool and the nuclear site at Burghfield, but the numbers of cases were small and there was no evidence of a consistent pattern or of a general increase near NPPs or other types of nuclear installation. When both the Welsh and English sides of the River Severn were considered, no significant increase was found near Oldbury.

The distribution of childhood leukaemia and other childhood cancers in Great Britain (COMARE, 2006) (geographical study)

3.15 The eleventh COMARE report (COMARE, 2006) analysed the general pattern of the incidence and clustering of childhood leukaemia and other childhood cancers in Great Britain as a whole. The study used the same database as that used in our tenth report, of over 32,000 cases of childhood cancer at ages up to 15 years, diagnosed between 1969 and 1993. Analyses were carried out at county, county district and ward level in relation to population data and socio-demographic variables, and showed that the underlying rates of these diseases were not uniform, but rather that there was a general tendency for clustering of cases to arise more often than would be expected by chance alone. The reasons for these variations are not clear.

3.16 Our eleventh report found higher incidence rates of acute lymphoblastic leukaemia (ALL) for children aged 1–4 years in rural wards with high diversity of incomers, which supports the hypothesis of an infectious aetiology relating to population mixing. The report also noted that ‘much attention has been given to infection/immune system based hypotheses almost to the exclusion of other possible explanations, which include other environmental agents, such as sources of pollution as well as aspects of genetic susceptibility. All of these hypotheses require further research’ (COMARE, 2006). Recently, McNally et al (2009) used the same dataset as used in our eleventh report with revised methodology and arrived at similar conclusions, suggesting that both genetic and environmental factors are likely to be involved, and that common infectious agents may be likely candidates in diseases such as ALL in children.

3.17 Our eleventh report concluded that the results from studies around nuclear installations should be viewed in the light of this non-uniformity in baseline rates of childhood cancer. It further recommended that ‘given the opinion in our tenth report (COMARE, 2005, paragraph 3.13) that the Sellafield and Dounreay excesses are unlikely to be due to chance’, the two sites should be kept under surveillance and periodic review.

Childhood leukaemia near British nuclear installations: methodological issues and recent results (Bithell et al, 2008, 2010) (geographical study)

3.18 Following publication of the results of the KiKK study on the risk of leukaemia among young children living near NPPs in Germany (Kaatsch et al, 2008a; Spix et al, 2008), Bithell et al (2008) conducted a study to re-examine the incidence of childhood leukaemia around NPPs in Great Britain; the paper should be read in conjunction with an amendment published in 2010 (Bithell et al, 2010). These papers used the same database as was considered previously in our tenth report and modified the methodology to apply a generally similar approach to that of the KiKK study, ie examining leukaemia incidence among children less than 5 years of age resident within 5 km of an NPP. Specifically, it compensated for the very small numbers of cases close to each site by performing a combined analysis for all 13 NPPs. It also extended the time period studied to cover 1969–2004; however, it concentrated solely on NPPs in Great Britain and did not include other nuclear installations. A Poisson regression model was used as this is the nearest equivalent to the conditional logistic regression used in the KiKK case–control study. The reciprocal of the distance was used as a regressor variable to measure proximity. Supplementary analyses were also performed for children under 5 years of age with acute leukaemia, where:

(i) the Poisson regression analysis was repeated using circles of varying radius (5, 10, 25 and 50 km);

(ii) incidence ratios in the 5, 10, 25 and 50 km circles were calculated for comparison with those in the KiKK study;

(iii) non-parametric tests such as those used for our tenth report were carried out.

3.19 The original paper (Bithell et al, 2008) made no correction for demographic factors, in order to make the results as comparable as possible with those of the KiKK study. Partly in response to a letter from Körblein and Fairlie (2010), the follow-up analysis (Bithell et al, 2010) corrected for population density determined at ward level. The results for the Poisson regression over 50 km circles showed that the regression coefficient was 0.46 ± 0.60 ($P = 0.22$) and for a 5 km circle the results were negative (-2.73 ± 2.70), indicating no positive association between childhood leukaemia and proximity to an NPP. This suggests that cases within this circle are not predominantly nearer to an NPP than would be expected from the distribution of the general population. With regard to incidence ratios, the study found no significant evidence for a higher incidence of acute leukaemia in children near to the NPPs in Great Britain, although the results suggested a slight effect within the 5 km circle (observed/expected, Obs/Exp = 1.36, 95% CI = 0.83–2.10, ie 20 observed cases versus 14.74 expected).

France

Overall mortality and cancer mortality around French nuclear sites (Hill and Laplanche, 1990) (geographical study)

3.20 Following the study of cancer mortality around nuclear installations in England and Wales (Forman et al, 1987), Hill and Laplanche (1990) conducted a similar study of cancer mortality rates during 1968–1987 in communities around six nuclear installations in France, of which four were NPPs. No significantly elevated SMR for leukaemia in the 0–24 year age group living within 16 km of an installation was found for any age or distance subgroup, or for the group of NPPs.

Leukaemia mortality around French nuclear sites (Hattchouel et al, 1995) (geographical study)

3.21 Hattchouel et al (1995) extended the study of Hill and Laplanche (1990) to cover leukaemia mortality during 1968–1989 around 13 French nuclear installations, of which 11 were NPPs. Again, no SMR was significantly elevated, and observed numbers of deaths were mainly less than expected.

Incidence of childhood leukaemia in the vicinity of nuclear sites in France, 1990–1998 (White-Koning et al, 2004) (geographical study) and Childhood leukaemia incidence below the age of 5 years near French nuclear power plants (Laurier et al, 2008a) (geographical study)

3.22 White-Koning et al (2004) investigated the incidence of acute leukaemia among children under 15 years of age living less than 20 km from one of the 29 major nuclear installations in France, of which 19 are NPPs and 10 are for other purposes, such as fuel reprocessing and research. Three of the research installations were treated together as a single site, due to considerable overlap of study areas. The study included all cases of acute leukaemia diagnosed between 1990 and 1998 within the installation areas. All 19 NPPs (Figure 3.2) commenced operation before the beginning of the study period, except for Golfech (1990), Penly (1990) and Civaux (1997). In addition to the year the plant commenced operation, the electrical power output of each of these sites was also considered. The study areas within 20 km radii were divided into concentric bands (0–5, 5–10, 10–15 and 15–20 km) and were constructed as aggregations of the communities (*communes*) with town halls situated within the defined zones. National registry data were used to derive annual expected numbers of cases for each age group and community under investigation.

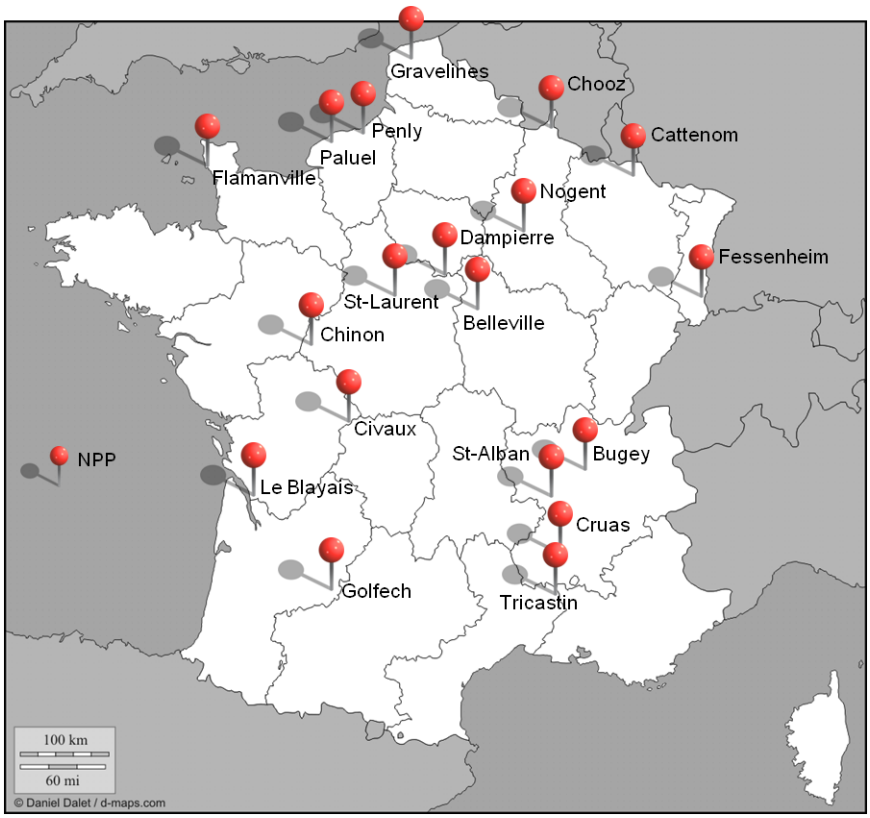

Figure 3.2 NPP sites in France

Map generated from image at D-maps.com (http://d-maps.com/m/france/france13.gif)

3.23 The relative risk of leukaemia was estimated by the SIR (observed to expected ratio), with 95% CIs for these ratios calculated using Byar's approximation (Breslow and Day, 1987). To investigate the existence of a decreasing trend in childhood leukaemia with increasing distance, three tests were applied to the data: (i) likelihood test, (ii) the LRS test based on the reciprocal of the distance, and (iii) Stone's Poisson maximum likelihood ratio (MLR) test. Analyses were carried out according to the type of site with three age groups (0–4, 5–9 and 10–14 years). Additional analyses were performed to consider potential variations according to the power output and the period of start-up. The study included a total of 670 observed cases of childhood leukaemia within the 20 km zones, and found no excess of childhood leukaemia near nuclear sites and no decrease of risk with increasing distance from the sites for all children or for any age group. For the NPPs only, there were 125 cases observed within 20 km of the sites against 137.01 expected, giving an SIR of 0.91. The test for detecting a decrease in SIR with increasing distance from the NPPs was not statistically significant. Similar conclusions were also obtained when the start-up year of the NPPs and their power output were taken into account.

3.24 This study, however, did not provide results that could be directly compared to those obtained by the KiKK study in Germany. Hence, an additional analysis was conducted by Laurier et al (2008a) focusing on leukaemia incidence among children below the age of 5 years in consecutive 5 km wide zones around the 19 NPPs in operation in France between 1990 and 1998. The study showed no decrease in SIR as a function of distance from the NPPs. The study also did not find an increase in leukaemia incidence in children under 5 years of age around French NPPs, although the number of cases was small (5 observed cases compared to the 5.2 expected from national rates within the inner 5 km zone, SIR = 0.96).

Childhood leukaemia incidence around French nuclear installations using geographic zoning based on gaseous discharge dose estimates (Evrard et al, 2006) (geographical study)

3.25 Evrard et al (2006) investigated the incidence of childhood acute leukaemia around French nuclear installations using a geographical zoning based on estimated doses to the red bone marrow due to gaseous radioactive discharges. The study included all children (aged 0–14 years) diagnosed with leukaemia between 1990 and 2001 who were living in the vicinity of nuclear sites at the time of diagnosis. The study area was defined as all *communes* (the smallest administrative unit in France) located in a 40 km^2 area centred on each of 23 French nuclear installations. There were four different types of nuclear installations in France: (i) 18 NPPs, (ii) two nuclear fuel cycle plants, (iii) one nuclear fuel reprocessing plant, and (iv) two research centres. Owing to the close proximity of the Tricastin NPP to the fuel conversion and fuel enrichment plant at Pierrelatte, they were considered as a single site (as a fuel cycle plant) throughout the study, resulting in the analysis of 18 NPPs compared with the 19 NPPs studied previously by White-Koning et al (2004).

3.26 The authors performed the analyses for the 23 sites, for all cases (0–14 years) and for the complete period, 1990–2001, and then separately by age group (0–4, 5–9 and 10–14 years), time period (1990–1995 and 1996–2001) and leukaemia type (ALL and AML). A zoning method based on radiation dose rather than distance was used and doses to the red bone marrow due to gaseous radioactive discharges were estimated. The authors used the SIRs to test for the existence of an increase in childhood leukaemia risk with increasing estimated radiation dose. No evidence was found for either a general increase or a trend in the incidence of childhood leukaemia over the full time period according to

this dose zoning in the vicinity of the 23 French nuclear installations, with 750 cases of childhood leukaemia in the studied areas against the 795 cases expected from national rates (although not a statistically significant deficit). There was also no evidence of a trend in SIR with the estimated doses for any of the three age groups, for any of the time periods, or for either of the leukaemia types. For the NPPs specifically, 242 cases were observed over the full time period against 253.03 expected (SIR = 0.96) and no significant trend of SIR with dose was found.

Spain

Leukemia, lymphomas, and myeloma mortality in the vicinity of nuclear power plants and nuclear fuel facilities in Spain (López-Abente et al, 1999) (geographical study)

3.27 López-Abente et al (1999) investigated mortality rates from haemato-logical and lymphatic cancers during 1975–1993 in towns lying within 30 km of 12 nuclear installations in Spain, of which seven were NPPs (Figure 3.3), in comparison with those of matched control towns lying 50–100 km from an installation. Relative risks (RRs), calculated as ratios of SMRs, were reported. For leukaemia mortality in the 0–24 year age group, the RR for towns within 15 km of an NPP was 1.2 (95% CI = 0.53–2.8), and no significant trend of RR with distance of residence within 30 km of an NPP was found.

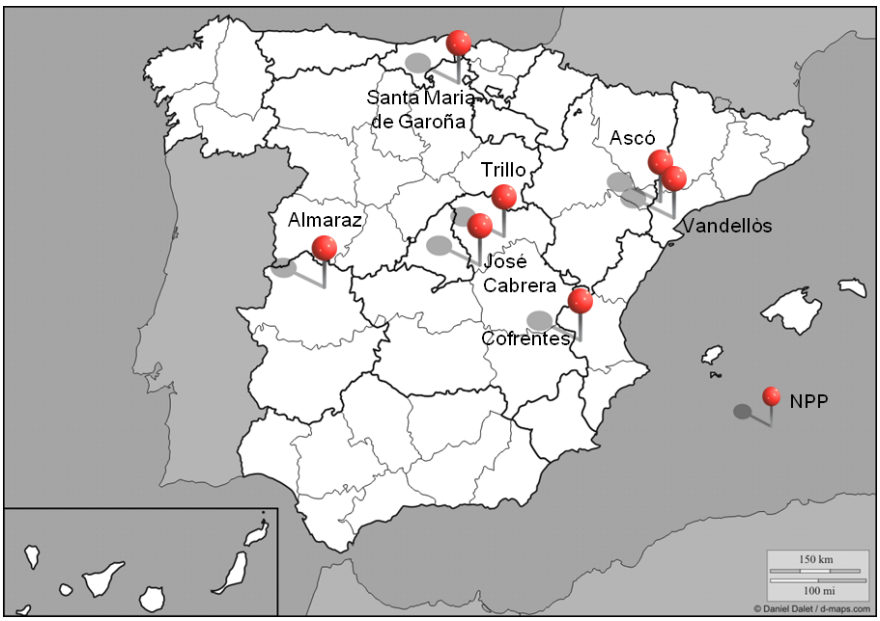

Figure 3.3 NPP sites in Spain

Map generated from image at D-maps.com (http://d-maps.com/m/espagne/espagne17.gif)

Sweden

Detection and assessment of clusters of disease: an application to nuclear power plant facilities and childhood leukaemia in Sweden (Waller et al, 1995) (geographical study)

3.28 As part of a general study of the distribution of childhood leukaemia incidence in Sweden, Waller et al (1995) examined the areas around four NPPs for the presence of leukaemia clusters among children under 16 years of age during 1980–1990 (Figure 3.4). No consistent evidence was found for childhood leukaemia clusters being related to proximity to an NPP, and the authors concluded that clusters of leukaemia among children were no more common near NPPs than elsewhere in Sweden.

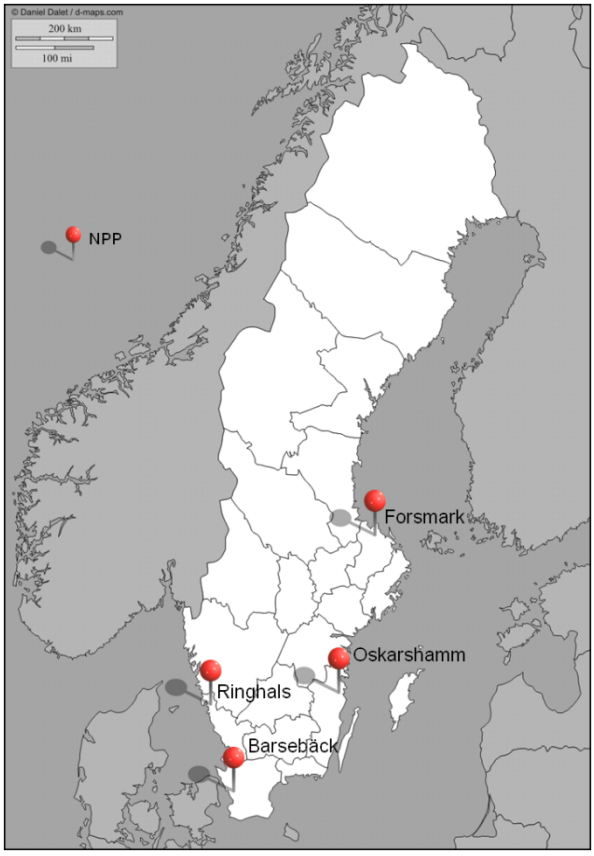

Figure 3.4 NPP sites in Sweden

Map generated from image at D-maps.com (http://d-maps.com/m/suede/suede13.gif)

Finland

Cancer incidence in the vicinity of Finnish nuclear power plants: an emphasis on childhood leukaemia (Heinavaara et al, 2010) (geographical, case–control and cohort studies)

3.29 Heinavaara et al (2010) investigated the incidence of overall cancer and leukaemia among children and adults living near the two Finnish NPPs, which are located on the coast (Figure 3.5). The main emphasis was concentrated on childhood leukaemia (ages 0–14 years). Three epidemiological study designs – geographical, case–control and cohort – were used to investigate whether living in the vicinity of NPPs increased the risk of childhood leukaemia.

3.30 The geographical analysis compared leukaemia and overall cancer incidence in areas within a 15 km radius of the two NPPs, and of three potential NPPs (planned to be constructed), with the rest of Finland. The numbers of leukaemia and overall cancer cases were obtained from the Finnish Cancer Registry by 5 year age group, sex and calendar year (during 1975–2004). The expected numbers were based on stratum-specific incidence in the rest of Finland. For the cohort analysis, residential details of people living near NPPs were assembled, based on census data; two cohorts were defined, the first was followed from 1981 to 2000 and the second was followed from 1991 to 2000. Leukaemia and overall cancer incidence in cohorts living within the 15 km radius area were compared with the reference group living in the 15–50 km radius area and the analysis adjusted for age and socioeconomic status. A case–control analysis with controls matched on sex, age and the area of residence at the time of diagnosis of the corresponding case was conducted for leukaemia using categorical distances. Residential histories of all study subjects were obtained from the Population Register Centre.

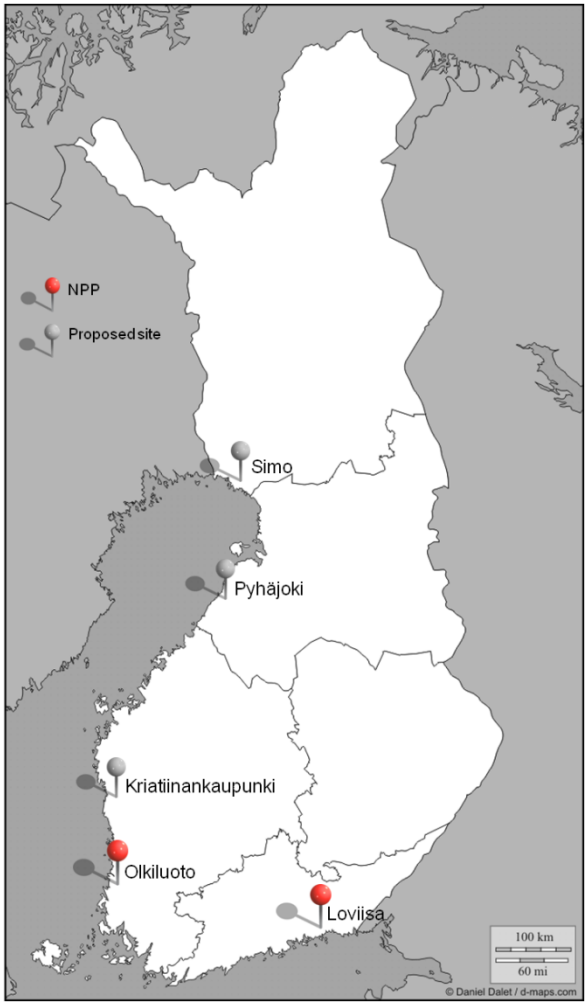

Figure 3.5 Current and planned NPP sites in Finland

Map generated from image at D-maps.com (http://d-maps.com/m/finlande/finlande13.gif)

3.31 For the geographical analysis, SIRs were calculated by taking the observed to expected ratio of leukaemia cases by time prior to and since the start of NPP operation (periods prior to start-up are, for Loviisa, 1975–1977, and for Olkiluoto, 1975–1979). For the cohort analysis, the indirectly standardised ratios (RRs) were calculated with adjustment for age and socioeconomic status. For the case–control analysis, the odds ratios (ORs) were calculated using conditional logistic regression. The primary analysis included children with average distance as an explanatory variable with an adjustment for parents' occupational radiation exposure. Both categorical distances (0–4, 5–9.9, 10–19.9, 20–29.9 and ≥30 km, with trend test) and continuous distances were used as explanatory variables in the analyses. The numbers of residencies between cases and controls were compared using Fisher's exact test and conditional logistic regression. All statistical tests of hypotheses were based on a two-sided 5% level of significance, with corresponding 95% CIs.

3.32 None of the methods indicated an increased risk of childhood leukaemia or of other cancers, either in the vicinity of the active NPPs or near the potential NPPs. In particular, there was no excess of childhood leukaemia in the closest inhabited area (the 5–9.9 km distance band) or a general trend in relation to distance from the two operating NPPs. The authors noted, however, that the small sample size of individuals living around the two NPPs, and the small number of cases, limited the strength of their conclusions. Geographical analysis and case–control analysis included 16 and 17 leukaemia cases, respectively, in

children below the age of 15 years in the 15 km zone, and there were only four and three cases for the 1980 and 1990 cohorts, respectively. No meaningful assessment could be made for the 5 km zone around the NPPs for leukaemia at 0–4 years of age due to the lack of cases. Results for adults did not show an increase in leukaemia and overall cancer incidence near operating NPPs, but overall cancer incidence in the vicinity of planned NPPs did appear to be increased in adults during 1974–2004.

USA

Cancer in populations living near nuclear facilities. A survey of mortality nationwide and incidence in two states (Jablon et al, 1991) (geographical study)

3.33 Jablon et al (1991) of the US National Cancer Institute investigated cancer mortality rates during 1950–1984 in counties containing or near nuclear facilities in the USA (Figure 3.6), in comparison with those of three control counties per installation county in the same region but remote from nuclear facilities. The ratios of rates in installation and control counties (the relative risk, RR) were determined. Cancer incidence was also investigated for four installations in (or adjacent to) two states with good quality cancer registration data; some of the control counties lay outside these states, so SIRs (rather than RRs) were used. Rates were calculated for counties before and after start-up of the relevant facility.

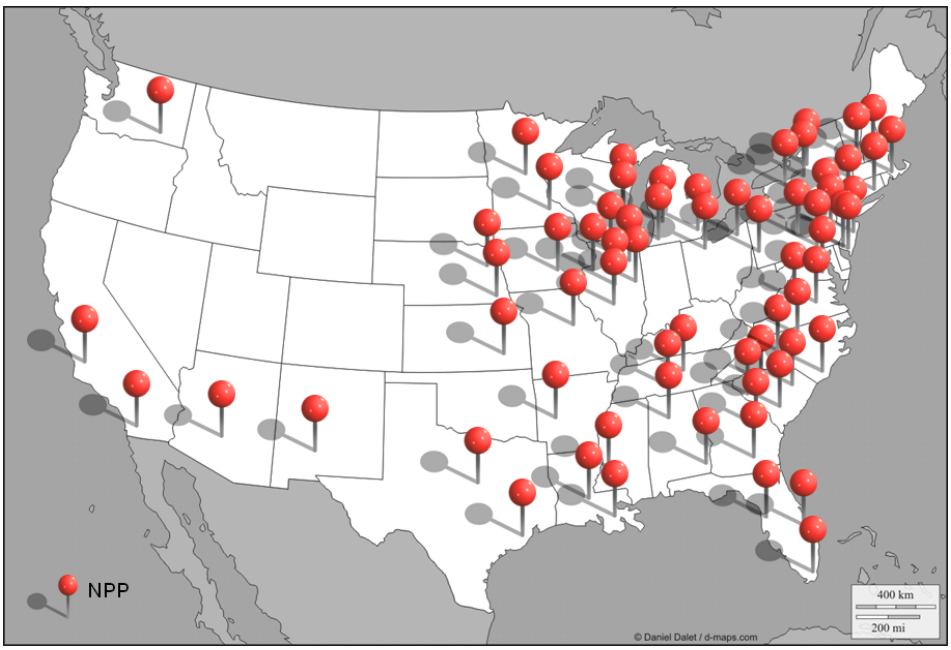

Figure 3.6 Current NPP sites in the USA

Map generated from image at D-maps.com (http://d-maps.com/m/usa/usa25.gif)

3.34 For all facilities, the childhood leukaemia (under 10 years of age) mortality RR was a significantly raised 1.08 before start-up and a non-significantly raised 1.03 after start-up; for the group of 52 NPPs, the RRs were 1.08 and 1.01, respectively. For childhood leukaemia incidence around the four NPPs included in the study, the SIR was a non-significant 1.13 before start-up and increased to a significant 1.36 after start-up, principally due to the significantly raised SIR of 1.55 for the Millstone NPP in Connecticut. The authors noted, however, that the childhood leukaemia SIR for Millstone was 1.34 in the 10 years before start-up, and that a childhood leukaemia and lymphoma cluster in the nearby town of Waterford had been investigated, but that 6 of the 11 cases had been diagnosed before start-up of the Millstone NPP.

3.35 Jablon et al (1991) concluded that if an increased risk of cancer and childhood leukaemia existed around nuclear facilities then it was too small to be detected by their study, but they noted that counties in the USA are large areal units and that mortality data are not as satisfactory as incidence data in the investigation of childhood leukaemia.

Canada

Childhood leukemia in the vicinity of Canadian nuclear facilities (McLaughlin et al, 1993) (geographical study)

3.36 McLaughlin et al (1993) examined childhood leukaemia (0–14 years of age) incidence (1964–1986) and mortality (1950–1987) rates for areas within 25 km of five nuclear facilities in Ontario, of which two are NPPs (Figure 3.7). For all facilities, the SMR was 1.17 (95% CI = 0.88–1.53) and the SIR was 1.07 (95% CI = 0.87–1.3), both by maternal residence at birth, and the SMR was 1.07 (95% CI = 0.86–1.3) by residence at death. The SMR by maternal residence at birth for the area around the two NPPs was reported as 1.40 (95% CI = 0.98–1.9), ie of marginal statistical significance; the SMR was lowest for the 0–4 year age group, at 1.4 (95% CI = 0.82–2.1).

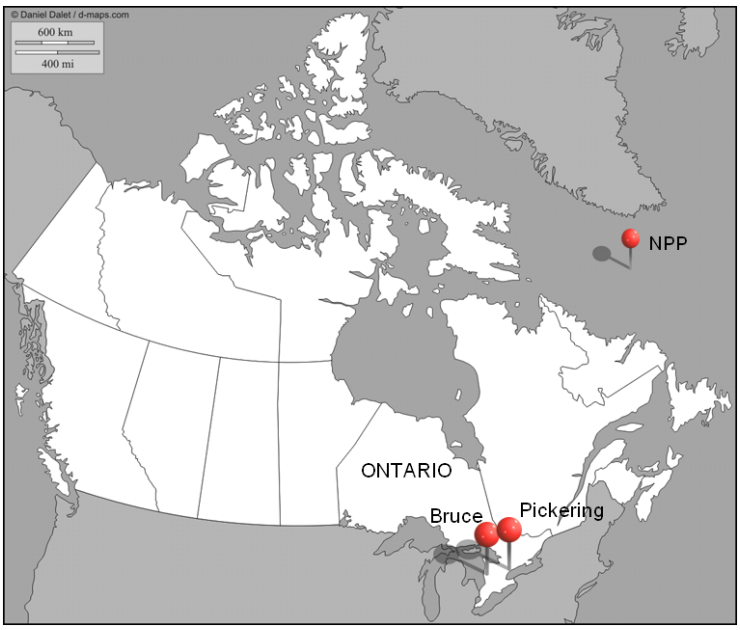

Figure 3.7 NPP sites in Ontario, Canada, considered by McLaughlin et al (1993)

Map generated from image at D-maps.com (http://d-maps.com/m/canada/canada21.gif)

Japan

Research on potential radiation risks in areas with nuclear power plants in Japan: leukaemia and malignant lymphoma mortality between 1972 and 1997 in 100 selected municipalities (Yoshimoto et al, 2004) (geographical study)

3.37 Yoshimoto et al (2004) examined leukaemia and lymphoma mortality rates during 1972–1997 in 20 municipalities in Japan containing 16 NPPs (Figure 3.8) (where an NPP site extended beyond a single municipality in four instances), in comparison with rates in 80 matched control municipalities. The 54 deaths from leukaemia among children (under 15 years of age) in the NPP municipalities gave an adjusted mortality rate that was almost exactly the same as that derived from the 221 deaths in the control municipalities.

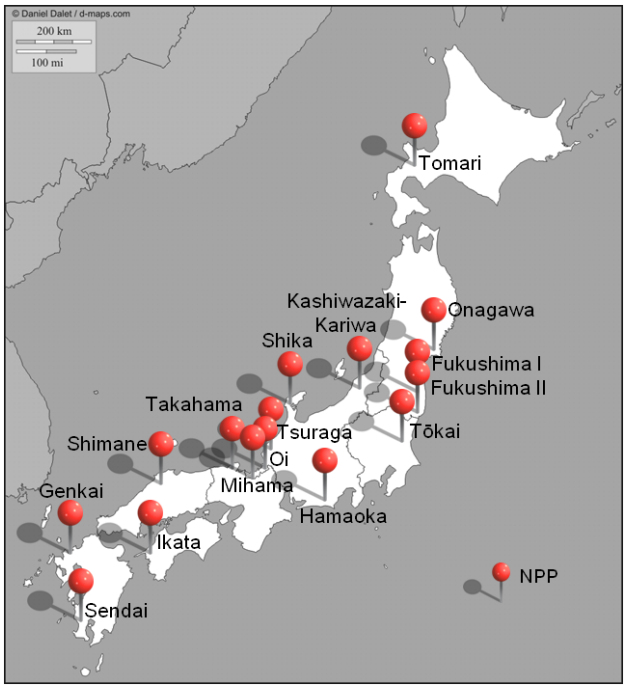

Figure 3.8 NPP sites in Japan

Map generated from image at D-maps.com (http://d-maps.com/m/japon/japon07.gif)

Summary

3.38 Studies conducted previously in Great Britain, including our tenth report (COMARE, 2005), found no significant evidence of raised risks of childhood cancer, or childhood leukaemia and NHL in particular, within 25 km of any NPP, or any increasing trend in incidence with proximity to an NPP.

3.39 The results of studies in other countries have supported the findings from Great Britain in reporting no general increase in childhood leukaemia rates near NPPs.

3.40 A further analysis of British data for the period 1969–2004, specific to leukaemia incidence among children aged 0–4 years living within 5 km of an NPP, again did not show any significantly increased risk.

ANNEX 3A

PROPOSED STUDIES ON THE RISK OF LEUKAEMIA IN YOUNG PEOPLE LIVING IN THE VICINITY OF NUCLEAR INSTALLATIONS

Switzerland

3A.1 A study is currently underway in Switzerland to determine if children who grow up near NPPs have an increased risk of developing childhood cancer, particularly leukaemia. The results of the study should be published in 2011.

3A.2 Switzerland has five NPPs (Beznau I and II, Mühleberg, Gösgen and Leibstadt – see Figure 3A.1), which generate about 40% of the electricity in Switzerland. Around 1% of the Swiss population (7.5 million) lives within 5 km of an NPP, with around 10% living within 15 km.

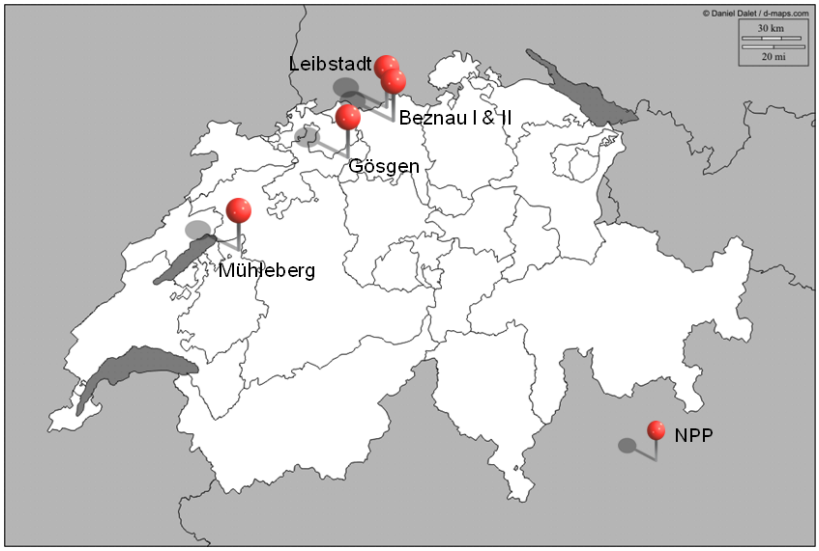

Figure 3A.1 Current NPP sites in Switzerland

Map generated from image at D-maps.com (http://d-maps.com/m/suisse/suisse07.gif)

3A.3 The CANUPIS study* is a national longitudinal study (a cohort study) that will include all children born between 1985 and 2007 in Switzerland. The lifetime residence histories of children who developed cancer will be compared with those of all other children in Switzerland. Cases will be determined from the Swiss Childhood Cancer Registry, which contains information on all children diagnosed with cancer in Switzerland since 1976. In total, 2957 children born between 1985 and 2007 were diagnosed with cancer, including 981 leukaemia cases.

3A.4 The CANUPIS study will use accurate information on place of residence, including geo-coded information on the exact place of the child's home rather than information on the location of the town or village of residence. The study

* http://www.canupis.ch/index.php?id=2116 (accessed December 2010).

will consider all places of residence since birth and thus should be able to examine the importance of exposures that occurred very early in childhood. Other environmental exposures that might be associated with an increased risk of cancer, such as high voltage power lines and industrial zones, will also be considered in the study. These factors may confound any association with living in the vicinity of NPPs.

USA

3A.5 At the request of the US Nuclear Regulatory Commission (USNRC), the National Academy of Sciences (NAS) is undertaking an assessment of cancer risks in populations living near USNRC-licensed nuclear facilities, which will be carried out in two consecutive phases. Phase 1 is a scoping study that will identify scientifically sound approaches for carrying out an epidemiological study of cancer risks. The 15 month scoping study began in September 2010. The result of this Phase 1 study will then be used to inform the design of the cancer risk assessment, which will be carried out in a future Phase 2 study.

3A.6 The USNRC is seeking the expertise of the NAS to update the 1990 US National Institutes of Health – National Cancer Institute (NCI) report, 'Cancer in Populations Living Near Nuclear Facilities'* (see Jablon et al, 1991). In the new study, the USNRC is also interested in having the NAS evaluate cancer diagnosis rates, as well as exploring how to divide the study areas around the facilities into geographical units smaller than the counties used in the earlier NCI report. The NCI report studied more than 900,000 cancer deaths from 1950–1984, using mortality records collected from counties that contain nuclear facilities. The researchers evaluated changes in mortality rates for 16 types of cancer in these counties from 1950 until each facility began operation, up until 1982. Cancer incidence data were only available for four facilities located in or adjacent to Iowa and Connecticut, due to the lack of cancer registration data for other states. The NCI report found no increased mortality risk from cancer for people living in the 107 counties in the USA containing, or closely adjacent to, 62 nuclear facilities, including all of the nuclear power plants operational before 1982.

* http://www.cancer.gov/cancertopics/factsheet/Risk/nuclear-facilities (accessed December 2010).

CHAPTER 4

REVIEW OF THE KiKK STUDY AND OTHER STUDIES ON THE RISK OF LEUKAEMIA IN YOUNG PEOPLE LIVING IN THE VICINITY OF NUCLEAR INSTALLATIONS IN GERMANY

Introduction

4.1 The results of a case–control study of cancer among young children living near nuclear power plants (NPPs) in western Germany, sponsored by the German government and called the *Kinderkrebs in der Umgebung von Kernkraftwerken* (KiKK) study, were published in late 2007 in two papers in scientific journals (Kaatsch et al, 2008a; Spix et al, 2008), together with a more detailed report (Kaatsch et al, 2007). The KiKK study follows two earlier geographical studies that examined childhood cancer incidence rates around German nuclear installations for the periods 1980–1990 (Michaelis et al, 1992) and 1991–1995 (Kaatsch et al, 1998); there is a considerable overlap between the time period for the KiKK study (1980–2003) and those covered by the previous geographical studies.

4.2 This chapter reviews both the recent KiKK study and earlier studies from Germany. This includes highlighting the assumptions made in these studies, the methodologies, and their strengths and weaknesses. In particular, it focuses on a detailed discussion of the KiKK study methodology and results. This chapter also considers a number of points regarding the KiKK study that were raised in a publication of the *Strahlenschutzkommission* (SSK, 2008), the German Commission on Radiological Protection, which considered the views of a group of independent international experts.

Geographical studies preceding the KiKK study in Germany

Incidence of childhood malignancies in the vicinity of West German nuclear power plants (Michaelis et al, 1992)

4.3 A study of childhood cancer incidence in the vicinity of nuclear installations in the former West Germany between 1980 and 1990 was carried out by Michaelis et al (1992). This was a geographical study of the incidence of cancer among children under 15 years of age who were diagnosed during 1980–1990 while resident in communities with at least one-third of their area lying within 15 km of any of 18 NPPs or of two major research reactors that commenced operations during 1960–1988. The study compared cancer registration rates in the surroundings of these 20 West German nuclear sites to those in the vicinities of 20 control locations. These control locations were the centres of communities randomly selected from rural districts that matched a given installation rural district by having, *inter alia*, a similar population density, the same urban/rural status and had a distance to the reference location of 30–100 km. Around each nuclear installation and control location communities defined by circles of 5, 10 and 15 km were considered as installation and control areas. The study also included six potential sites for NPPs (ie areas where sites were selected for the construction of an NPP, but the plant was not built).

4.4 Details of cancer cases from 1980 to 1990 were obtained from the West Germany Registry of Childhood Malignancies and included a total of 1610 cases diagnosed before 15 years of age. For the six installations that had started operation after 1 January 1980, the inclusion of cases from the installation area and its control area was restricted to those diagnosed at least one year after start-up. Population data were taken from the 1987 census and annual updates. Age-adjusted expected numbers for an area were calculated using reference registration rates for West Germany.

4.5 Standardised incidence ratios (SIRs) were computed for the regions surrounding the nuclear installations (SIR_I) as well as for the control regions (SIR_C) by calculating the ratios of observed and expected numbers of cases. Relative risks (RRs) were calculated by dividing SIR_I by SIR_C and 95% CIs by using a method equivalent to that described by Breslow and Day (1987). To assess the impact of potential confounding factors not controlled by geographical matching, data were collected from self-administered questionnaires issued by physicians to the families of children diagnosed during the sub-period 1986–1990 with acute leukaemia, non-Hodgkin lymphoma, neuroblastoma and Wilms' tumour. These data related to various medical, lifestyle, occupational and environmental factors.

4.6 The study found no statistically significantly raised RR for cancers overall or acute leukaemia specifically, among those under 15 years of age living in the <15 km zone during 1980–1990 – the main hypothesis under study. The authors did, however, observe a statistically significantly raised RR for acute leukaemia among those younger than 5 years of age living in the <5 km distance zone (RR = 3.01, 95% CI = 1.25–10.31, P = 0.015, based on 19 cases in the installation areas and 5 cases in the control areas). However, the SIR_I for this subset of data is not unusual, 1.26 (95% CI = 0.78–1.93), and the raised RR is largely driven by the significantly low SIR_C of 0.42 (95% CI = 0.15–0.93).

4.7 Michaelis et al (1992) also presented results for the period of start-up of an installation: before 1970, 1970–1980 and after 1980. The raised RR for acute leukaemia among young children under 5 years of age resident in the <5 km zone is confined to installations that commenced operations before 1970: RR = 7.09 (P = 0.021, based on 12 cases in the installation areas and 1 in the control areas). The SIR_I is not especially remarkable, at 1.58 (95% CI = 0.86–2.69), whereas the SIR_C is notably low, at 0.22 (95% CI = 0.01–1.08).

4.8 The study also showed that the RR for acute leukaemia around potential sites was similar to that found around active nuclear installations when using the same control regions: a significantly raised RR of 4.16 (95% CI = 1.23–17.23, P = 0.020) for acute leukaemia among young children under 5 years of age resident within the 5 km zone (see Keller et al, 1992). However, the SIR_I is 1.75 (95% CI = 0.71–3.64) so that, as with active installations, the raised RR is primarily due to the low SIR_C.

4.9 From the responses to the questionnaire survey, Michaelis et al (1992) decided that there was insufficient evidence of a material difference in the influence of potential background risk factors between installation and control areas for a formal analysis adjusting for potential confounding factors to be conducted.

4.10 In discussing their results, Michaelis et al (1992) highlighted the raised RR for acute leukaemia among young children under 5 years of age resident in communities within 5 km of a major nuclear installation in West Germany. However, they also drew attention to the exploratory nature of this particular

subgroup analysis and to the influence of the significantly low SIR_C in generating this finding. Their provisional conclusion was that the low SIR_C had occurred by chance, which would also largely account for the raised RR. Finally, Michaelis et al (1992) suggested that a case–control study should be considered to further explore their findings.

An extended study on childhood malignancies in the vicinity of German nuclear power plants (Kaatsch et al, 1998)

4.11 A second geographical study (Kaatsch et al, 1998) was conducted to extend the study of incidence rates of childhood cancer in the vicinity of German NPPs. The main aim of this study was to assess whether the results from the original study (Michaelis et al, 1992) for 1980–1990 persisted for the later time period 1991–1995. The study design was similar to that in the original study, and cases were identified from the German Childhood Cancer Registry (GCCR). However, the treatment of control areas was slightly different from that of Michaelis et al in that the control SIRs were always calculated using all of the communities with at least one-third of their areas lying within 15 km of the control location rather than using only those communities within the respective distance zones (ie not just those communities within the 5 km and 10 km distance zones when the inner zones were being considered, as was done by Michaelis et al. Kaatsch et al also investigated childhood cancer incidence near three major nuclear installations in the former German Democratic Republic (GDR or East Germany) and in German communities lying within 15 km of three NPPs sited in France and Switzerland.

4.12 For all cancers and acute leukaemia among children under 15 years of age resident in communities lying within 15 km of a major nuclear installation in the former West Germany, the study failed to show a significantly increased SIR. For acute leukaemia among children under 15 years of age resident in the <5 km distance zone, Kaatsch et al (1998) drew attention to the Krümmel NPP near Hamburg, with an RR of 4.07 (95% CI = 1.33–12.45).

4.13 For acute leukaemia among children under 5 years of age living in the <5 km distance zone, for which Michaelis et al (1992) found a significantly raised RR during 1980–1990, the study found a non-significantly raised SIR_I of 1.43 (95% CI = 0.77–2.43: Keller et al, 1992) and a non-significantly raised RR of 1.39 (95% CI = 0.69–2.57, based on 12 cases in the installation areas and 75 cases in the control areas). The authors examined the influence on this result of the four cases near the NPP at Krümmel, which was well known as being a recognised excess (Schmitz-Feuerhake et al, 1993); when the Krümmel site was excluded from the analysis, the RR for the remaining 19 plants was reduced to an unremarkable 1.01 (95% CI = 0.42–2.09).

4.14 For installations where operations began before 1970, for which Michaelis et al (1992) found a significantly raised RR for acute leukaemia among children under 5 years of age living in the <5 km zone during 1980–1990, the equivalent RR during 1991–1995 was non-significantly decreased (RR = 0.63, 95% CI = 0.12–2.00). The findings for areas around nuclear installations in the former East Germany and in areas of Germany near NPPs located in other countries were not unusual. Kaatsch et al (1998) did not give any results for areas near potential sites of NPPs.

4.15 Kaatsch et al (1998) noted that the change in the control area from communities within 5 km of the control location to those within 15 km of this location led to greater stability of the SIR_C and therefore of the RR. The authors further noted that if the control areas had been communities lying within 5 km

of a control location, as in the study of Michaelis et al (1992), rather than within 15 km, the RR for acute leukaemia among young children under 5 years of age in the <5 km zone for all sites would have remained non-significantly raised at 2.00 (95% CI = 0.66–7.26). The authors concluded from their study that no further investigations were necessary at that time.

Study of clustering of childhood leukaemia in Germany

Spatial clustering and space–time clusters of leukemia among children in Germany, 1987–2007 (Schmiedel et al, 2010)

4.16 Schmiedel et al (2010) investigated clustering of childhood leukaemia in Germany. The study considered 11,946 cases (0–14 years of age) for the period 1987–2007 at the municipality level, using one statistical test to investigate general clustering and another to search for localised clusters. None of the analyses showed any evidence of a general tendency to clustering of leukaemia cases and, in particular, no evidence of clustering was determined for ALL or for the 2–5 year old age group. Localised clusters were also not observed. It was noted that the use of municipalities was a limitation for the study as these varied in population size from one child to more than 430,000 children – moreover, large municipalities could not be subdivided. This is in contrast to the 'ward' units used in the eleventh COMARE report (COMARE, 2006). The size of area investigated may explain why the clusters noted around NPPs in the KiKK study are not detected at the aggregated municipality level in this investigation and also why the general clustering found in the eleventh COMARE report was not detected in Germany. However, geographical studies of childhood leukaemia incidence around NPPs in Germany also did not find clustering around NPPs with the exception of the Krümmel NPP (see below), and it is notable that the study of Schmiedel et al (2010) apparently did not detect this cluster, even though a marked excess of cases was found in the two municipalities closest to the Krümmel NPP by geographical studies.

Excess incidence of childhood leukaemia around the Krümmel NPP

4.17 A notable excess of cases of childhood leukaemia in the community of Elbmarsch close to the Krümmel NPP in northern Germany was first reported in the early 1990s (Schmitz-Feuerhake et al, 1993). The excess started in 1990, with three cases being recorded, and has persisted in Elbmarsch and in the neighbouring community of Geesthacht until at least 2005 (Grosche et al, 1999; Hoffmann et al, 1997, 2007); during 1990–2005 ten cases of leukaemia were diagnosed in children under 5 years of age while resident within 5 km of the Krümmel NPP, which is around five times the number expected on the basis of German national rates (Hoffmann et al, 2007). Laurier et al (2008b) have assessed this excess of cases around Krümmel to be one of three confirmed childhood leukaemia clusters near nuclear installations, the other two being at Seascale near Sellafield and in the vicinity of Dounreay – that is, it may reasonably be judged that the cluster in the vicinity of Krümmel is indicative of an underlying raised risk of childhood leukaemia in the area rather than being a chance fluctuation.

4.18 Undoubtedly, the Krümmel excess is pronounced and must be taken into account when assessing the incidence of childhood leukaemia around German nuclear installations as a group from 1990 onwards, as was recognised by Kaatsch et al (1998) in their geographical study of childhood cancer incidence around nuclear installations in Germany during 1991–1995 (ie after the commencement of the Krümmel cluster). The influence of Krümmel was also recognised in the KiKK study and the subsequent geographical study (Kaatsch et al, 2008b), covering the period 1980–2003.

4.19 The Krümmel cluster was readily detected by geographical studies: Kaatsch et al (1998) presented data for the incidence of acute leukaemia among young children under 5 years of age living within 5 km of a nuclear installation during 1991–1995, from which an SIR of 5.71 (95% CI = 1.82–13.78) may be derived for Krümmel. By way of comparison, Hoffmann et al (2007) reported for children under 5 years of age living in the two communities located <5 km from Krümmel NPP during 1990–1998 an SIR of 5.39 (95% CI = 1.98–11.72, based on six observed cases), while for 1999–2005 the SIR was 4.33 (95% CI = 1.18–11.09, based on four observed cases).

Case–control studies preceding the KiKK study in Germany

The Northern Germany Leukaemia and Lymphoma (NLL) study (Hoffmann et al, 2003, 2008)

4.20 The Northern Germany Leukaemia and Lymphoma (NLL) study was a population-based case–control study that investigated incident cases of malignant haematological and lymphatic diseases diagnosed during 1986–1998 for people less than 75 years of age and resident in six rural districts around Hamburg, with reference to two controls per case selected from population registries and individually matched on sex, age and residential area (Hoffmann et al, 2008). The NLL study was conducted largely because of the concern generated by the report of a marked excess of cases of childhood leukaemia that had occurred since 1990 in the vicinity of the Krümmel NPP, an area included in the NLL study (Hoffmann et al, 2007, 2008).

4.21 Radiation doses arising from routine discharges of radioactive material from the four NPPs in the NLL study area were reconstructed from information obtained from face-to-face interviews in combination with assessed inhalation and ingestion doses for each study subject, and took into account individual residential histories (Hoffmann et al, 2003). Medical radiation exposures were also assessed (Hoffmann et al, 2008). This is in contrast to the KiKK study (see paragraphs 4.23–4.57), which relied upon the distance to the residence at diagnosis as a proxy for cumulative dose.

4.22 The NLL study did not find systematically increased risks for any grouping of leukaemia and lymphoma associated with the radiation doses assessed to have been received as a result of routine discharges from the NPPs (Hoffmann et al, 2003). In particular, the NLL study could not explain the excess of childhood leukaemia in the vicinity of the Krümmel NPP in terms of the assessed doses arising from routine radioactive discharges (Hoffmann et al, 2007).

The KiKK study

Epidemiological study of childhood cancer in the vicinity of nuclear power plants (the 'KiKK study') (Kaatsch et al, 2008a; Spix et al, 2008)

Introduction

4.23 The KiKK study was a population-based case–control study, which commenced in 2003 and was carried out by researchers from the German Childhood Cancer Registry (GCCR), based at the University of Mainz, of the risk of cancer among young children diagnosed between 1 January 1980 and 31 December 2003 while under 5 years of age, resident near a major nuclear installation in Germany and registered with the GCCR. Following the earlier geographical studies of Kaatsch et al (1998) and Michaelis et al (1992), public concern in Germany over the risk of leukaemia among young children living near NPPs had been intensified by a self-published report of childhood cancer incidence near NPPs in Bavaria, which had attracted media publicity (Deutsches Ärzteblatt, 2001), and the German Government decided to fund a further investigation. The design of the KiKK study was agreed after discussions between the GCCR and an expert committee established by the *Bundesamt für Strahlenschutz* (BfS, the Federal Office for Radiation Protection).

4.24 The BfS expert committee selected the larger and longer running German nuclear facilities to be the subject of the KiKK study, which resulted in the inclusion of 16 NPPs in the former West Germany. A power plant was considered to be relevant for study from one year after commencement of electricity generation until five years after cessation of operations. Two NPPs (Lingen and Emsland) were built on adjacent sites, but had different (non-overlapping) operating periods, so that the study area was composed of 16 NPPs at 15 sites. Figure 4.1 shows the locations of the NPPs in the study.

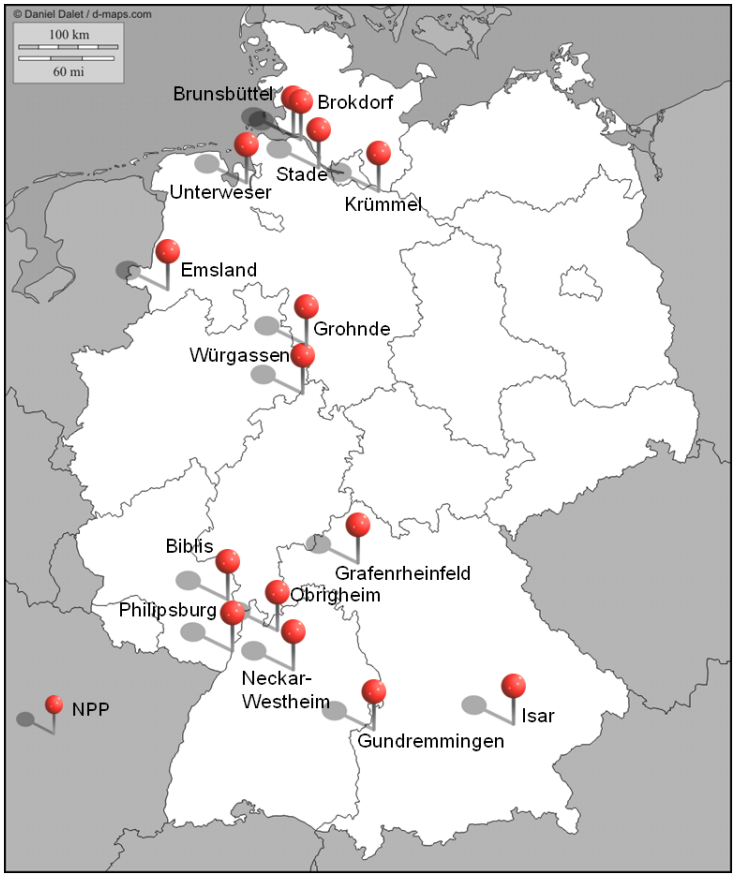

Figure 4.1 Locations of German NPPs in the KiKK study (Kaatsch et al, 2008a)

Map generated from image at D-maps.com (http://d-maps.com/m/allemagne/allemagne13.gif)

4.25 The BfS committee then selected appropriate study areas in the vicinities of these NPPs, with an emphasis on the east of the plants because of the prevailing westerly winds in Germany. For each NPP, the rural district (*Landkreis*) containing the plant, the immediately neighbouring rural district and usually one more rural district to the east were selected, although occasionally a fourth rural district was included to obtain appropriate coverage of the areas that had been included in the earlier geographical studies of Michaelis et al (1992) and Kaatsch et al (1998); these rural districts defined the area for a specific NPP. An administrative district in Germany is either an 'urban district' (*Kreisfreie Städte*), consisting of a city, or a geographically larger 'rural district' (*Landkreis*), a district containing a varying number of towns and villages that form the smaller administrative units of communities/municipalities (*Gemeinden*). Urban districts were excluded from the study regardless of their location with respect to an NPP, while some communities in the study area were far (>70 km) from the nearest NPP (Kaatsch et al, 2008b). A 'rural district' may contain small or medium sized towns and Kaatsch et al (2008a) noted that communities/municipalities fall into three classes: 'urban', 'mixed' and 'rural',

but that this classification applies to the whole community so that an outlying settlement might be defined administratively as part of a nearby town and be classed as 'urban', despite its possibly rural character. Overall, the study area consisted of a total of 41 rural districts.

4.26 Among young children less than 5 years of age, 1592 registered cases of cancer with a known residential address at diagnosis were living in the study area at the time of diagnosis during the study period relating to the nearest NPP (see paragraph 4.23). All case children were matched with control children selected from the records of the appropriate registrar's office. Each German community has a resident registration office (*Einwohnermeldeamt*), which provides a mechanism for accurately determining age- and sex-specific populations on an annual basis at the small-area level. Apart from for one state, there is no central registration of residency, so that each of the communities included in the KiKK study – over 1000 in total – was contacted separately for the purposes of control selection. The controls were matched for date of birth (as closely as possible, but within 18 months), sex and residence in the specific NPP area at the time of diagnosis. For the selection of each control, a community was chosen at random from the appropriate study area, weighting communities by the size of the population of children of the same sex and age as the case in the year of diagnosis. The authorities in this community were then requested to make available names and addresses of candidate control children, and from this list the controls closest to the date of birth of the case were selected; but not all communities were willing to provide candidate controls. Six controls per case were requested and three of these were selected at random for the principal analysis. In the final analysis 4735 controls were used.

4.27 For all case and control children, the geo-code of the place of residence at the time of diagnosis was obtained from the state (*Land*) register. For 9.9% of the case children and 8.4% of the controls, the actual residential address could not be coded and was replaced by the geo-code of the street midpoint (140 cases and 359 controls) or by the geo-code of the centroid of the community or postcode area (20 cases and 40 controls). The position of the chimney of each NPP was similarly coded from high resolution maps. This allowed the distance of a residence from the nearest relevant NPP to be computed, which could be estimated usually with a precision of around 25 m.

4.28 To assess the possible influence of confounding, the families of a subset of all cases and controls were invited to participate in a structured telephone interview enquiring about potential risk factors for childhood cancer; the biological mother was interviewed whenever possible. The subset included all cases with a selected diagnosis (leukaemia, lymphoma or a central nervous system, CNS, tumour) diagnosed during 1993–2003, and their matched controls. The questions related to a total of 20 potential confounding factors: socio-economic status, information on radiation exposure (parents or child), other factors (eg pesticides and mother's hormone intake), immune system related issues (such as vaccinations, breast feeding and child's social interaction), type of region, and folic acid intake during pregnancy. In addition, enquiries were made about previous residences of the child.

4.29 The main question addressed by the KiKK study was whether there was a monotonically decreasing relationship between the distance of the place of residence at the time of diagnosis from the nearest NPP included in the study at that time and the risk of childhood cancer. In essence, this study involved comparing the distances from the NPP to the residences of the affected children with those of the matched control children; a conditional logistic regression model with the reciprocal of distance (in kilometres) – the 'proximity' – used as a

continuous independent variable in the model: log(odds ratio) = 1 + β/x, where x is the distance in kilometres from the NPP and β is the estimated parameter (regression coefficient). The justification for this $(\text{distance})^{-1}$ assumption is given as the dispersion models presented in the UNSCEAR 2000 Report, Annex A (UNSCEAR, 2000), which give the concentrations in air of radionuclides released to the atmosphere by distance from the NPP, although the relationships presented by UNSCEAR are actually functions of $(\text{distance})^{-1.2}$ for the noble gases and tritium, and $(\text{distance})^{-1.4}$ for carbon-14.

4.30 One-sided tests of statistical significance were conducted on the basis that low level radiation is unlikely to be beneficial. For all leukaemias combined, the possibility of a quadratic model (second order polynomial) was investigated and assessed by the Akaike information criterion; if this fitted better than the untransformed model, the quadratic model was applied to the groupings of subtypes of leukaemia. For each model, the regression coefficient, β, was estimated and the lower one-sided 95% confidence limit (lower one-sided 95% CL) was determined.

4.31 In addition, categorical analyses were performed for the inner 5 km and 10 km distance zones versus the corresponding outer zones. The results of the categorical models and the continuous model were compared by calculating the corresponding odds ratio (OR) from the continuous model, using the mean proximity of the controls in the corresponding inner zone. The conditional logistic regression model included one proximity measure at a time (continuous or categorical) and no other covariates.

4.32 The primary analysis included all cases of cancer in children less than 5 years of age at the time of diagnosis. The diagnostic groups defined in advance in the study protocol and for which separate analyses were conducted were leukaemia (described by the diagnostic groups for leukaemia of the International Classification of Childhood Cancer version 3, ICCC Ia–e), acute lymphoblastic leukaemia (ICCC Ia), acute non-lymphatic leukaemia (ICCC Ib), central nervous system tumours including medulloblastoma (ICCC IIIa–f) and embryonal tumours except for medulloblastoma (ICCC IVa, V and VIa). In further subgroup analyses, the operating periods of the NPPs were divided into two groups of earlier and later periods, and the study subjects were confined to those who were eligible to be interviewed. All regression results were presented with lower one-sided CLs at a statistical significance level of 5%.

4.33 The effect of selecting three matched controls from the maximum of six controls was assessed by repeating the regression analysis using all available (up to six) controls. The appropriateness of the fitted curve was investigated by fractional polynomial and Box-Tidwell models for assessing the best fitting curve (based on the statistical deviance). Further sensitivity analyses were conducted in addition to those planned beforehand. While, overall, 10% of communities refused to provide control addresses, the proportion was higher (16%) among communities situated in the inner 5 km zone. Therefore, the relevant analyses were repeated only for cases (and their matched controls) from communities which provided control addresses.

4.34 The questionnaire part of the study (relating to cases of leukaemia, lymphoma and CNS tumours diagnosed during 1993–2003, and their matched controls) raised a ‘strong suspicion’ in the research group that communities might have sent the addresses of candidate control children who were never resident in the respective community before the time of diagnosis of the corresponding case (about 5%). The effect of this was assessed using datasets generated by removing this 5% of control children from the analysis, assuming

this 5% of controls were either randomly distributed with respect to distance from the NPP, or more likely to live near to it or remote from it.

4.35 For a sub-sample of controls (45%) a check could be made on the address at the time of diagnosis of the corresponding case and, among these, 15% of controls were found not to have lived at the supplied address at the time (although they might have lived there prior to the time of diagnosis of the corresponding case). The analysis was repeated excluding those controls with an address at the time of diagnosis of the matched case child that had been found to be incorrect.

4.36 Previous German studies had shown that specific NPPs, notably Krümmel, could have a substantial influence on results (see paragraphs 4.17–4.19), so the continuous analysis was repeated omitting sequentially from the analyses individual NPPs. To assess the impact of potential confounding factors the intention was to use a change by more than one standard deviation (in the calculation for the respective subset of cases not including any confounder variables) of the continuous proximity parameter to identify such factors.

4.37 The correctness of the computations was checked by having them repeated independently by a statistician at the coordinating centre of clinical trials (KKS) of the University of Mainz.

4.38 Given the results of the previous geographical studies (Kaatsch et al, 1998; Michaelis et al, 1992), attention was focused upon the risk of leukaemia within 5 km of an NPP. In recognition of the periods covered by the geographical studies (1980–1990 by Michaelis et al and 1991–1995 by Kaatsch et al), analyses were conducted for the sub-periods 1980–1990, 1991–1995 and 1996–2003, the last sub-period being the only one using data that had not been included in a previous study.

Results

4.39 The characteristics of the case and control children included in the KiKK study (all cancers in young children under 5 years of age and resident in the study area at the time of diagnosis during 1980–2003, and their matched controls) were presented in the paper by Spix et al (2008). The study included a total of 1592 children diagnosed with any cancer during 1980–2003 and 4735 controls (matched on sex, age and the NPP area of residence at the time of diagnosis of the corresponding case). Of these, 593 cases were children with leukaemia. As expected, the age and sex distributions (matching criteria) were similar. The case children lived from 1.2 to 81.6 km from the nearest NPP and the control children between 1.1 and 92.0 km; within the <5 km zone the mean distance of a residence of a case child from an NPP was 3.2 km, while that for a control child was 3.1 km.

4.40 For all cancers, the regression coefficient, β, from the continuous conditional logistic regression model (see paragraph 4.29) for the measure of proximity was 1.18 (lower one-sided 95% CL = 0.46), based on 1592 cases and 4735 controls. For the diagnostic groups defined in the study protocol, only leukaemia showed a statistically significant effect, β = 1.75 (lower one-sided 95% CL = 0.65), based on 593 cases and 1766 controls; the regression coefficient for all cancers other than leukaemia was not statistically significant (β = 0.76, lower one-sided 95% CL = –0.20), nor were the regression coefficients for the predefined subgroups of CNS tumours and embryonal tumours (β = –1.02, lower one-sided 95% CL = –3.40, and β = 0.52, lower one-sided 95% CL = –0.84, respectively). The regression coefficient for all cancers was significantly raised for the earlier operating period of the NPPs, β = 1.89 (lower one-sided 95% CL = 0.85), but not for the later period, β = 0.54 (lower one-sided 95% CL = –0.47),

although the difference is not statistically significant. The effect in the subgroup eligible for interviewing was similar to that for the study as a whole, although the coefficient was not statistically significant because of the small numbers involved (β = 1.05, lower one-sided 95% CL = –0.30, based on 471 cases and 1402 controls).

4.41 When the continuous model for all cancers was refitted with a maximum of six controls per case, the regression coefficient remained the same as that obtained previously with three selected controls per case (β = 1.18, lower one-sided 95% CL = 0.50, based on 1592 cases and 8527 controls). When the model was refitted after exclusion of cases from communities that did not provide control addresses, and their matched controls (leaving 1310 cases and 3905 controls), the regression coefficient was reduced, but remained statistically significant (β = 1.01, lower one-sided 95% CL = 0.24); for leukaemia, the change in the regression coefficient was small, from 1.75 to 1.73.

4.42 When 5% of all controls were excluded either randomly from the dataset with respect to their distances from the nearest NPP, or selectively from close to or far from the nearest NPP, to simulate the potential influence of mismatched controls, average regression coefficients, β, of 1.18, 1.54 and 1.09, respectively, were found, based on 1000 simulations each, and these estimates remained statistically significant. Further, excluding from the analysis those control children whose residential address at the time of diagnosis of their matched case child had been checked and found to be incorrect produced a regression coefficient, β, of 1.05 (lower one-sided 95% CL = 0.07, one-sided P-value = 0.04: Kaatsch et al, 2007), which is of marginal statistical significance at the one-sided 5% level.

4.43 For leukaemia, the residences of 8.6% of the 2359 study subjects could not be geo-coded, so the geo-code of the midpoint of the street or the centroid of the community had to be used as a surrogate. Kaatsch et al (2008a) considered that this was unlikely to have a material impact on the results.

4.44 Sequentially omitting each NPP from the continuous analyses yielded statistically significant regression coefficients that were close to the overall estimate. For leukaemia, the maximum reduction occurred when Krümmel was omitted: the regression coefficient changed from 1.75 to 1.39 (lower one-sided 95% CL = 0.14) and remained statistically significant.

4.45 Fractional polynomial modelling and the Box-Tidwell model both suggested that an alternative measure of proximity of the form $(\text{distance})^{-0.5}$ would fit slightly better than $(\text{distance})^{-1}$, but not significantly so. For all leukaemias, a linear–quadratic model did not fit significantly better than a linear model, so only a linear model was fitted to the data for leukaemia subtypes.

4.46 The categorical analyses showed a statistically significant effect for children living in the <5 km zone, OR = 1.61 (lower one-sided 95% CL = 1.26) for all cancers. Considering the various diagnostic groups, a significant effect was again found only for leukaemia (OR = 2.19, lower one-sided 95% CL = 1.51, based on 37 cases within the 5 km zone); residence in the <10 km zone had a smaller effect (OR = 1.18, lower one-sided 95% CL = 1.03). The fitted curve from the continuous model for all malignancies predicted similar ORs for the <5 km and <10 km zones to those obtained from the categorical analysis. For leukaemia, when the <5 km zone is compared with the remainder of the study area (≥5 km) in a categorical analysis, the resulting OR of 2.19 (lower one-sided 95% CL = 1.51) compares with the OR for this zone when using the continuous model of 1.76 (lower one-sided 95% CL = 1.24).

4.47 Spix et al (2008) inferred that, based on the result of the categorical analysis, 29 out of the total number of 77 observed cases of cancer among young children (38%, 95% CI = 24%–61%) diagnosed while living in the <5 km zone during 1980–2003 may be attributed to the fact that they were resident in this zone. Kaatsch et al (2008a) inferred that of the 37 cases of leukaemia resident at the time of diagnosis in the <5 km zone, 20 cases could be attributed to residence in this zone.

4.48 Spix et al (2008) compared the findings of the KiKK case–control study with those of the previous geographical studies of childhood cancer in the vicinity of major nuclear installations in West Germany for all cancers (under the age of 5 years and living within 5 km of an NPP). The authors divided the years by the previous study periods (1980–1990 and 1991–1995) and the new study period (1996–2003). The observed effect estimate in the earliest period, 1980–1990, resulting from the case–control study was statistically significant (OR = 1.99, lower one-sided 95% CL = 1.33), while the estimates for the periods 1991–1995 and 1996–2003 were not statistically significant and were similar (OR = 1.41, lower one-sided 95% CL = 0.90, and OR = 1.45, lower one-sided 95% CL = 0.96, respectively). From the earlier geographical studies, relative risks for 1980–1990 and 1991–1995 of 1.43 (95% CI = 0.89–2.43) and 0.97 (95% CI = 0.50–1.89), respectively, were found.

4.49 Kaatsch et al (2008a) conducted a similar comparison for leukaemia (see Table 4.1). For the period 1980–1990, the categorical OR from the case–control study was again statistically significant (OR = 3.00, lower one-sided 95% CL = 1.54, based on 13 cases within 5 km of an NPP). This estimate was similar to the relative risk estimate reported in the geographical study for the same period (Michaelis et al, 1992). For the period 1991–1995, the OR was also found to be statistically significant, but in the geographical study the relative risk estimate for this period was not statistically significant. For the new study period 1996–2003, the OR was of marginal statistical significance at the one-sided 5% level (OR = 1.78, lower one-sided 95% CL = 0.99).

Table 4.1 Results for childhood leukaemia under 5 years of age for residence within 5 km of an NPP from the KiKK case–control study and from previous geographical studies in Germany using different study periods (reported in Kaatsch et al, 2008a)

	Case–control study (the KiKK study)		Previous geographical studies	
Study period	Number of cases	Categorical OR (lower one-sided 95% CL)	Number of cases	Relative risks § (95% CI)
1980–1990	13	3.00 (1.54) *	19	3.01 (1.25–10.31) ‡
1991–1995	10	2.10 (1.04) *	12	1.39 (0.69–2.57)
1980–1995	23	2.53 (1.57) *	31	1.49 (0.98–2.20)
1996–2003	14	1.78 (0.99) †	–	–
1980–2003	37	2.19 (1.51) *	–	–

* Statistically significant at the one-sided 5% level.
† Marginally statistically significant at the one-sided 5% level.
‡ Statistically significant at the two-sided 5% level.
§ Ratio of two standardised incidence ratios.

4.50 Spix et al (2008) noted that information on residences of the child prior to that at the time of diagnosis could not be used in the KiKK study because of 'poor and selective participation in the questionnaire part of the study'. The questionnaire involved children diagnosed with leukaemia, lymphoma or a CNS tumour during 1993–2003 and their matched controls. The authors considered that substantial self-selection had occurred among those who participated in the questionnaire survey, such that those who were interviewed were not representative of the study population as a whole, particularly with respect to the distance of residence from an NPP. This meant that participation bias was a distinct possibility. It was noted, however, that the inclusion of the information that was available from the interviews on potential confounding factors did not alter the distance parameter estimate by more than one standard deviation.

4.51 Kaatsch et al (2008a) reported that the response rates in the questionnaire survey varied 'remarkably' by distance from an NPP: the overall response was 78% for cases and 61% for controls, while the response for the inner 5 km zone was 63% for cases and 45% for controls. The authors considered that 'no conclusions on the relationship between potential confounders and the reported findings can be drawn'.

4.52 Spix et al (2008) considered that the sensitivity analyses they had conducted demonstrated that the various problems encountered with the selection of controls were small and had not introduced serious biases into the KiKK study. They noted that the specificity of the effect for leukaemia indicated that the results were unlikely to be accounted for by deficiencies in control selection. They also pointed out that their findings were not driven by any one NPP. Kaatsch et al (2008b) reiterated the view of the KiKK study research group that the 'problems with control recruitment may have led to slight overestimation of the effect', but not serious errors.

4.53 Kaatsch et al (2008a) considered that the case–control approach of the KiKK study was preferable to the previous geographical studies because the distance of a residence from an NPP could be determined for each individual in the study. Spix et al (2008) noted, however, that the distance of residence from the nearest NPP at the time of diagnosis is 'a crude surrogate for potential exposure to radiation' since 'it does not account for topography, weather, vegetation, differences in background radiation, other sources of individual exposure to radiation or the time actually spent by the individual in the home'.

4.54 In a geographical study, Kaatsch et al (2008b) reported that the SIR for the group of communities with centroids lying within the inner 5 km zone was 1.41 (95% CI = 0.98–1.97), which is of marginal statistical significance at the two-sided 5% level, while the SIRs for the groups of communities with centroids lying in the outer distance zones were found to be not statistically significant and in general close to 1.0.

4.55 Kaatsch et al (2008b) noted that

> 'Dividing the communities whose central points lay in the 5-km zone by type of settlement, the SIR was 1.81 (CI 0.73 to 3.72, based on 7 cases of disease) for rural localities, 1.18 (CI 0.69 to 1.90, 17 cases) for mixed settlements, and 1.71 (CI 0.82 to 3.14, 10 cases) for urban areas. None of these SIR values are statistically significantly elevated, and no trend is discernible.
>
> 'Evaluation of the case–control study showed a clear-cut increase in risk for cases from rural localities. Nevertheless, the estimator for the OR of the 5-km zone varied hardly at all after adjustment for these variables (2.21 vs 2.19). Thus the observed effect cannot be explained by the fact that NPP are preferably located in rural areas.'

Reviews of the KiKK study by others in the literature

Strahlenschutzkommission (SSK, the German Commission on Radiological Protection) review of the KiKK study (SSK, 2008)

4.56 Soon after the results of the KiKK study were published, the German Commission on Radiological Protection (*Strahlenschutzkommission*, SSK) asked a group of international experts for an independent review of the KiKK study and that report was published in autumn 2008 (SSK, 2008). Although the experts confirmed the increased relative risk of leukaemia in children under 5 years of age living within 5 km of an NPP, they also commented on a number of issues associated with methodological aspects of the study, including study design – in particular, the use of distance as a surrogate for radiation exposure from an NPP, problems in selecting appropriate controls, the failure to take account of residential histories, and other factors that could be responsible for an elevated risk of leukaemia around NPPs, such as population mixing – in relation to the interpretation of the results.

4.57 The authors of the KiKK study assessed the level of exposure to radiation arising from the operation of the NPPs simply in terms of the distance between the residence at the time of diagnosis and the plant, assuming doses decreased as a function of the reciprocal of this distance. Although detailed data for discharges of radioactive substances from NPPs and consequent doses were available, these were not taken into consideration in the KiKK study. The SSK report gives effective doses from discharges of between 0.0001 mSv and 0.02 mSv per year for individual NPPs, which were published by the German Parliamentary Reports for various years of the period covered by the KiKK study. The SSK report also notes that these doses are substantially lower than doses from other radiation sources in Germany. For example, the average effective dose from medical diagnostic radiation exposure per person is 1.9 mSv per year and natural background radiation exposure gives an average individual effective dose of 2.1 mSv per year (95% CI = 1.2–4.6 mSv).

4.58 Further, the SSK report compared the findings of the Oxford Survey of Childhood Cancers (OSCC) for the risk of childhood leukaemia and other childhood cancers following *in utero* exposure to radiation resulting from maternal X-ray examinations with those of the KiKK study. The OSCC found that the relative risk for children younger than 5 years of age is 1.4 both for leukaemia and for other cancers after receiving a foetal dose of around 10 milligray (mGy). In contrast, the KiKK study found relative risks of 1.61 for all types of cancer and 2.19 for leukaemias among children under 5 years of age living within 5 km of an NPP, where individual doses from discharges would be much less than the equivalent foetal dose of 10 mGy. The SSK report concluded that the reason for the increased risk of leukaemia in young children found in the KiKK study was unclear, but that the increase cannot be explained by the level of ionising radiation received from discharges from the NPPs.

Assessment of the KiKK study: re-examination of the KiKK data by the researchers from the University of Oxford (SSK, 2009)

4.59 Professor Sarah Darby and Dr Simon Read of the University of Oxford were asked to conduct an independent analysis of the raw data of the KiKK study. This analysis was published as a chapter of the full SSK report (SSK, 2009). Darby and Read were able to confirm the results of the calculations reported by Kaatsch et al (2008a); however, they also carried out some new analyses with a different approach from that of the KiKK study investigators.

4.60 The findings from their analysis were based on the data for acute leukaemia rather than ‘all leukaemia’ and used two-sided 5% levels of statistical

significance with corresponding 95% confidence intervals. In the categorical assessment, the distance band 10–29 km from an NPP was chosen as the reference category, having the largest number of cases and controls to maximise statistical power. Non-overlapping distance categories around NPPs were also considered. Further, separate analyses were carried out with data from the earliest study period (1980–1990, used as the hypothesis-generating period) and with data from the later time period (1991–2003, used as the hypothesis-testing period). From this analysis Darby and Read reached the following conclusions.

(i) The findings of the KiKK study were confirmed.

(ii) The exclusion of six cases of chronic leukaemia made little difference to the regression coefficient obtained with the continuous logistic regression model of the KiKK study (Kaatsch et al, 2008a); the regression coefficient obtained was 1.70 (95% CI = 0.39–3.02, P = 0.01).

(iii) The increased risk of acute leukaemia in young children indicated by this continuous model was 'entirely due' to the risk in the <5 km distance zone, where the categorical OR was 2.27 (95% CI = 1.45–3.56, P = 0.0003). For distance zones ≥5 km, 'no evidence of any increase' was found.

(iv) When the <5 km zone was compared with the remainder of the study area (ie the ≥5 km area as a single zone) for the three sub-periods, the odds ratio was greatest and statistically significant in the earliest period, 1980–1990 (OR = 3.00, 95% CI = 1.36–6.62, P = 0.007), ie during the hypothesis-generating period. However, the odds ratio was less and not statistically significant in the other two periods: for 1991–1995 the OR was 2.10 (95% CI = 0.91–4.83, P = 0.08) and for 1996–2003 the OR was 1.78 (95% CI = 0.89–3.57, P = 0.10). When these two periods are considered together (ie 1991–2003), the odds ratio becomes statistically significant (OR = 1.90, 95% CI = 1.12–3.25, P = 0.02).

4.61 Darby and Read also repeated the sensitivity analysis carried out in the KiKK study, examining acute leukaemia in the <5 km and ≥5 km zones during 1980–1990 and 1991–2003, but excluding cases (and their matched controls) from those communities where the authorities had declined to cooperate fully in the requested supply of data on candidate control children. In order to increase statistical power, they also used all six controls matched to a case from communities that did cooperate fully with the KiKK study rather than just the three chosen for the primary analyses of Kaatsch et al (2008a). The OR for 1980–1990 was increased (OR = 3.20, 95% CI = 1.56–6.60, P = 0.002), but the OR for 1991–2003 was decreased in strength (OR = 1.74, 95% CI = 1.02–2.96, P = 0.04) and was of only marginal statistical significance.

4.62 Darby and Read conducted further analyses of the KiKK study data in terms of residence at the time of diagnosis in an urban or rural area (or a mixed urban/rural area), as already classified by the KiKK study investigators. As anticipated, the zone within 5 km of an NPP tends to be more rural than the study area as a whole. In control children, 22% who lived within 5 km of an NPP were from rural areas and 50% and 28% from mixed and urban areas, respectively; this compares with 16%, 41% and 43% in these groupings for children resident in the rest of the study area.

4.63 For the entire 1980–2003 period, the odds ratio for acute leukaemia among children living in mixed urban/rural areas (OR = 0.99, 95% CI = 0.74–1.34, P = 0.96) was essentially the same as that for children living in urban areas (the reference category), but the odds ratio for children living in rural areas

was significantly raised (OR = 1.85, 95% CI = 1.06–3.23, P = 0.03). The odds ratio for rural areas was greater during 1991–2003 (OR = 2.22, 95% CI = 1.14–4.34, P = 0.02), which Darby and Read considered to be the hypothesis-testing period.

4.64 Of interest is that this increased odds ratio for rural children during 1980–2003 is due to incidence among boys aged 2–4 years (OR = 2.85, 95% CI = 1.23–6.59, P = 0.01), corresponding to the peak of incidence of acute lymphoblastic leukaemia in childhood (although Darby and Read did not subdivide acute leukaemia).

4.65 When the zone within 5 km of an NPP was considered, taking the reference category as children living in urban or mixed urban/rural areas in the ≥5 km zone, odds ratios were found to be the greatest for rural areas in the period 1980–1990 (see Table 4.2) and for the entire period 1980–2003 (OR = 5.14, 95% CI = 1.98–13.29, P = 0.001), although the odds ratio was also raised for combined urban and mixed urban/rural areas in the <5 km zone, significantly so for 1980–2003 and 1991–2003 (see Table 4.2).

4.66 Darby and Read also highlighted evidence from Germany and Great Britain for an increased risk of childhood leukaemia in areas where NPPs had been planned but not built, which was of a similar magnitude to the increase observed in the vicinities of operating plants, indicating that 'nuclear power plants tend to be built in areas where the risk of childhood leukaemia is already increased for some other, and as yet un-established, reason'.

4.67 Darby and Read concluded that 'there is indeed a causal factor present in the environment that varies in magnitude according to the location of the child's residence', and that their analysis of the KiKK study data in terms of the nature

Table 4.2 Estimated odds ratios for acute leukaemia in children aged under 5 years according to distance of place of residence from an NPP and urban/rural status, separately for the hypothesis-generating and hypothesis-testing periods and also for the entire study period (taken from SSK, 2009)

Study period	Distance from NPP and urban/rural status	Number of cases	Number of controls	OR (95% CI)	P-value
Hypothesis-generating period 1980–1990	<5 km and rural	6	5	7.57 (1.70–33.66)	0.008 *
	≥5 km and rural	24	161	1.14 (0.42–3.07)	0.80
	<5 km and mixed/urban	7	21	2.19 (0.88–5.49)	0.09
	≥5 km and mixed/urban	153	907	1 †	
Hypothesis-testing period 1991–2003	<5 km and rural	4	15	3.11 (0.83–11.69)	0.09
	≥5 km and rural	60	276	2.18 (1.19–4.00)	0.01 *
	<5 km and mixed/urban	17	49	1.89 (1.04–3.42)	0.04 *
	≥5 km and mixed/urban	227	1457	1 †	
Entire study period 1980–2003	<5 km and rural	10	20	5.14 (1.98–13.29)	0.001*
	≥5 km and rural	84	437	1.85 (1.11–3.09)	0.02 *
	<5 km and mixed/urban	24	70	1.96 (1.19–3.23)	0.008 *
	≥5 km and mixed/urban	380	2364	1 †	

* Two-sided statistical significance at the 5% level.
† Baseline category.

of the area in which children were living at the time of diagnosis was evidence for the importance of urban/rural status. Moreover, 'The increased risk of childhood leukaemia associated with living in a rural area did not in itself account for the increased risk associated with living near a nuclear power plant. However, it is likely that living in a rural area is not in itself the causal factor, but that it is associated with the true, but as yet unknown causal factor. Such a factor, which must exist, may well be responsible for both associations.'

4.68 Finally, Darby and Read noted that their analysis of the KiKK study data involved only a small proportion of the population of children in Germany, and that a more extensive analysis might provide further evidence of the importance of residential location on the risk of leukaemia in young children.

Leukaemia in young children living in the vicinity of nuclear power plants (Little et al, 2008)

4.69 Little et al (2008) produced an editorial review in relation to the results of the KiKK study. The authors pointed out three potential explanations for this finding:

(i) It could be a chance observation, which has persisted, but is possibly diminishing in these areas of Germany for an unknown reason. The authors noted that the spatial and space–time distributions of leukaemia and other childhood cancers derived from the large study conducted in Great Britain (COMARE, 2006) were observed to be non-random.

(ii) Radiation exposure might be much higher for some individuals living in these areas than could be inferred from the available measurements.

(iii) The Kinlen hypothesis could be correct and infections may cause some cases of leukaemia (Kinlen, 1988), or an alternative but unknown casual factor exists and was expressed in the study areas.

4.70 The authors discussed other risk factors that could play a role in the development of childhood leukaemia, including possible genetic susceptibility and low level environmental exposure from non-ionising radiation, such as from mobile phones and their base stations. Finally, the authors recommended the conduct of multilevel methods of analysis to strengthen the investigation of exposures.

The 'Kinderkrebs in der Umgebung von Kernkraftwerken' study: results put into perspective (Grosche, 2008)

4.71 Grosche (2008), from the German Federal Office for Radiation Protection (BfS), gave a brief description of the KiKK study and discussed some issues regarding this study.

(i) On the issue of the critical importance of choosing the age of the children in this context, the author noted that taking all internationally published studies together 'there seems to be no increased risk for all children below the age of 15', but that the KiKK study shows elevated risk towards younger ages of less than 5 years, suggesting a lower risk among children aged 5–14 years.

(ii) Grosche noted the decreasing trend with distance over time, suggesting that this may be explained by an active agent, the prevalence of which decreases over time; this agent may be related to the situation before and after the start-up of the NPPs.

(iii) The author described the significant relative risks for children under the age of 5 years within the inner 5 km distance zone as compared to the non-significant findings for the other distance categories, and questioned whether this means an unknown agent causes earlier onset of disease close to the sites among vulnerable children who would otherwise have developed leukaemia later.

(iv) Grosche pointed out that the risk near potential sites should also be investigated further, as both the German and British studies show some evidence of an increase in the risk of childhood leukaemia near these sites.

(v) Finally, the author noted that the radiation exposure of the public due to discharges from NPPs is very low, a factor of about 1000 too low to explain the reported effect.

Comparison of case–control and geographical study findings for the time periods and area boundaries defined in the KiKK study

4.72 Table 4.3 shows the estimated categorical odds ratios (OR) and relative risks (RR – the ratio of standardised incidence ratios, SIR) for leukaemia among children under 5 years of age living within 5 km of an NPP, when compared to leukaemia among young children living more than 5 km from an NPP. The ORs were derived from the case–control analysis by the KiKK study investigators (Kaatsch et al, 2008a); the SIR values were based on the geographical study conducted by Kaatsch et al (2008b), with additional data provided to COMARE by the KiKK study investigators. The RRs and associated 95% CIs were calculated using a method described by Breslow and Day (1987)*. The results in Table 4.3 are presented by different study periods and by different NPP groupings, as including all NPPs, all NPPs except the Krümmel plant, and the Krümmel plant alone. The Krümmel NPP was considered separately because it was already known that a pronounced excess of childhood leukaemia had occurred in the vicinity of this plant during 1990–2005 (Hoffmann et al, 2007).

4.73 Based on the case–control analysis of the KiKK study, the highest estimated OR was observed in the earliest study period, 1980–1990: for all NPPs, the OR was highly statistically significant (3.00, lower one-sided 95% CL = 1.54); exclusion of Krümmel from this grouping reduced the OR slightly, but the OR of 2.78 (lower one-sided 95% CL = 1.42) remained highly statistically significant. It is of note that the single case occurring <5 km from Krümmel during 1980–1990 was diagnosed in 1990 and marked the start of the Krümmel cluster. For the period 1991–1995, the estimated OR for all NPPs was again found to be statistically significantly raised (OR = 2.10, lower one-sided 95% CL = 1.04), but the exclusion of Krümmel reduced the OR to 1.79 (lower one-sided 95% CL = 0.76), which was not statistically significant. A similar pattern was found for 1996–2003, when the grouping of all NPPs produced a marginally significantly raised OR of 1.78 (lower one-sided 95% CL = 0.99), while with Krümmel excluded the OR reduced to a non-significant 1.52 (lower one-sided 95% CL = 0.81). For the whole period 1980–2003, the OR for all NPPs was significantly elevated at 2.19 (lower one-sided 95% CL = 1.51), and the exclusion of Krümmel reduced the OR to a still significant 1.96 (lower one-sided 95% CL = 1.31).

4.74 The influence of Krümmel during the period 1991–2003, when a marked excess of childhood leukaemia was known to have occurred in the vicinity of the NPP, is only to be expected. Specific matched ORs for the Krümmel <5 km zone versus the ≥5 km zone have not been published, but case and control numbers

* This estimates the logarithm of the ratio in a model using the binomial distribution of the two counts conditional on their total; this 'exact' procedure avoids the need for the simultaneous estimation of an average value of the SIR.

for the <5 km and ≥5 km zones supplied by the KiKK study investigators have permitted the calculation of unmatched ORs for Krümmel. These unmatched ORs for Krümmel must be treated with caution due to the small numbers involved, but the unmatched ORs for all NPPs and all NPPs except Krümmel are similar to the matched ORs (see Table 4.3), and the unmatched OR for Krümmel during 1991–2003 of 4.75 (95% CI = 1.48–15.21) clearly reflects the known excess risk in this area during this period.

4.75 What is noteworthy is the significantly raised OR of 2.78 (lower one-sided 95% CL = 1.42) for all NPPs except Krümmel during 1980–1990; ORs for this NPP grouping during 1991–1995 and 1996–2003 are raised, but not significantly so (see Table 4.3). Apart from the results for Krümmel in the periods following 1980–1990, this OR for all NPPs except Krümmel during 1980–1990 is influential in producing the significantly raised OR for all NPPs during the entire study period 1980–2003 of 2.19 (lower one-sided 95% CL = 1.51), which is the main finding of the KiKK study.

4.76 The results of the geographical study of Kaatsch et al (2008b), which followed as closely as possible the spatial and temporal structure of the KiKK case–control study, allow the calculation of some SIRs for the <5 km distance zone and the remainder of the study area ≥5 km from an NPP. These published data have been augmented by additional data supplied by the University of Mainz giving observed and expected numbers of leukaemia cases for these two zones during the three periods considered by the KiKK study. Using these data, a full set of SIR values, and relative risks (RRs) computed from the ratios of SIRs for the <5 km zone and the ≥5 km zone, may be calculated and these are also given in Table 4.3.

4.77 The SIRs for the <5 km zone around Krümmel give a clear indication of the known excess of cases in this area from 1990 onwards: for 1991–2003 the SIR for the inner distance zone is 3.85 (95% CI = 1.68–7.61) and the RR is 6.03 (95% CI = 2.10–15.50). By way of comparison, the SIR for the <5 km zone during 1991–2003 for all NPPs except Krümmel is 1.09 (95% CI = 0.62–1.79) and the RR is 1.15 (95% CI = 0.62–1.96), which are unexceptional. The equivalent unmatched categorical ORs for 1991–2003 are 4.75 (95% CI = 1.48–15.21) for Krümmel and 1.58 (95% CI = 0.87–2.89) for all NPPs except Krümmel, which are compatible with the RR values.

4.78 For the NPP grouping of all plants except Krümmel, the ORs and RRs for 1991–1995 and 1996–2003 are consistent and unremarkable (see Table 4.3). However, for all NPPs except Krümmel during 1980–1990, both the matched OR of 2.78 (lower one-sided 95% CL= 1.42) and the unmatched OR of 2.79 (95% CI = 1.25–6.21) are statistically significantly raised, but both the SIR for the inner zone of 1.38 (95% CI = 0.72–2.42) and the RR of 1.29 (95% CI = 0.66–2.32) are far from being statistically significant. As noted in paragraph 4.75, together with the ORs for Krümmel during 1991–1995 and 1996–2003, the OR for all NPPs except Krümmel during 1980–1990 is influential in producing the statistically significantly raised OR for all NPPs during the whole study period 1980–2003. Although the difference between the OR and the RR for all NPPs except Krümmel during 1980–1990 is not formally statistically significant, the interpretation of the OR is likely to differ from that of the RR and, given the role of this particular OR in generating the overall OR obtained by the KiKK study, this difference deserves attention.

Table 4.3 Comparison of the odds ratios (ORs) from the KiKK study with the relative risks (RRs) from an equivalent geographical study for leukaemia in children under 5 years of age living <5 km and ≥5 km from an NPP during 1980–2003 and three sub-periods

		KiKK case–control study							Geographical study mirroring the areas considered in the KiKK study ¶						
		<5 km from NPP		≥5 km from NPP		Categorical matched $OR_{<5km}$ vs $OR_{\geq 5km}$ from NPP † (lower one-sided 95% CL) ‡	Categorical unmatched $OR_{<5km}$ vs $OR_{\geq 5km}$ from NPP §		<5 km from NPP			≥5 km from NPP			Relative risk $SIR_{<5km}$ vs $SIR_{\geq 5km}$ from NPP (two-sided 95% CI)
Time period	NPP grouping	No. of cases *	No. of controls *	No. of cases *	No. of controls *		OR (lower one-sided 95% CL) ‡	(two-sided 95% CI)	Obs *	Exp *	SIR (two-sided 95% CI)	Obs *	Exp *	SIR (two-sided 95% CI)	
1980–2003	All plants	37	54	556	1712	2.19 (1.51)	2.11 (1.48)	(1.38–3.24)	34	24.09	1.41 (0.98–1.97)	585	599.58	0.98 (0.90–1.06)	1.44 (0.99–2.04)
	All except Krümmel	29	45	534	1600	1.96 (1.31)	1.93 (1.29)	(1.20–3.11)	26	21.54	1.21 (0.79–1.77)	560	565.82	0.99 (0.91–1.08)	1.22 (0.79–1.81)
	Krümmel	8	9	22	112	N/A	4.53 (1.86)	(1.57–13.01)	8	2.55	3.14 (1.35–6.18)	25	33.76	0.74 (0.48–1.09)	4.24 (1.65–9.70)
1980–1990	All plants	13	14	211	649	3.00 (1.54)	2.86 (1.50)	(1.32–6.17)	13	9.40	1.38 (0.74–2.37)	226	212.21	1.06 (0.93–1.21)	1.29 (0.68–2.26)
	All except Krümmel	12	13	203	613	2.78 (1.42)	2.79 (1.43)	(1.25–6.21)	12	8.67	1.38 (0.72–2.42)	217	203.43	1.07 (0.93–1.22)	1.29 (0.66–2.32)
	Krümmel	1	1	8	36	N/A	4.50 (0.40)	(0.25–79.83)	1	0.73	1.37 (0.03–7.63)	9	8.78	1.02 (0.47–1.95)	1.34 (0.03–9.64)
1991–1995	All plants	10	15	141	435	2.10 (1.04)	2.06 (1.03)	(0.90–4.68)	9	5.7	1.58 (0.72–3.00)	144	147.07	0.98 (0.83–1.15)	1.61 (0.72–3.19)
	All except Krümmel	6	10	136	406	1.79 (0.76)	1.79 (0.75)	(0.64–5.02)	5	5.01	1.00 (0.32–2.33)	139	138.38	1.00 (0.84–1.19)	1.00 (0.32–2.37)
	Krümmel	4	5	5	29	N/A	4.64 (1.19)	(0.92–23.48)	4	0.69	5.80 (1.58–14.8)	5	8.69	0.57 (0.19–1.34)	10.07 (1.99–46.8)
1996–2003	All plants	14	25	204	628	1.78 (0.99)	1.72 (0.98)	(0.88–3.38)	12	8.93	1.34 (0.69–2.35)	215	239.35	0.90 (0.78–1.03)	1.49 (0.76–2.68)
	All except Krümmel	11	22	195	581	1.52 (0.81)	1.49 (0.80)	(0.71–3.13)	9	7.80	1.15 (0.53–2.19	204	222.96	0.91 (0.79–1.05)	1.26 (0.57–2.44)
	Krümmel	3	3	9	47	N/A	5.22 (1.20)	(0.91–30.11)	3	1.13	2.65 (0.55–7.76)	11	16.39	0.67 (0.33–1.20)	3.96 (0.71–15.0)

* Values not available in Kaatsch et al (2008b) were provided by the KiKK study investigators.
† Odds ratio (OR) estimates reported by Kaatsch et al (2008a).
‡ Lower one-sided 95% confidence limit (equivalent to the lower limit of a two-sided 90% CI).
§ Unmatched OR estimates calculated by COMARE.
¶ Standardised incidence ratio (SIR) estimates calculated by COMARE where not available in Kaatsch et al (2008b).
N/A Not available.

Critique of the KiKK study

4.79 Although case–control studies have some advantages over cohort studies – and in particular over geographical studies – in that they are individually-based studies for which it is often possible to obtain detailed information for each study subject, they are nevertheless vulnerable to a number of different biases, including selection bias and participation bias. In particular, it is important to obtain controls that are as closely as possible representative of the population from which the cases are drawn, but this often proves difficult.

4.80 Considerable efforts were made by the KiKK study investigators to ensure that a representative sample of matched control children was obtained from the population registries of the communities falling within the study area; but the authorities in some communities declined to cooperate in the supply of candidate controls, and a disproportionate number of these communities were near NPPs. When Darby and Read (SSK, 2009) excluded cases (and their matched controls) from communities that did not cooperate with the KiKK study team, they found in their analysis of acute leukaemia for all NPPs, an OR for the <5 km zone versus the ≥5 km zone during 1980–1990 (the hypothesis-generating period) of 3.20 (95% CI = 1.56–6.60), while during 1991–2003 (the hypothesis-testing period) the OR was 1.74 (95% CI = 1.02 – 2.96), ie of marginal statistical significance, although it must be borne in mind that the period 1991–2003 will be influenced by the presence of the excess of leukaemia cases near the Krümmel NPP.

4.81 Rather than population-based controls, as in the KiKK study, some case–control studies use other sources of controls, such as patients without the index disease attending the same hospitals as the cases. A possible alternative set of controls for leukaemia cases in the KiKK study is that of the other cancer cases (see Table 4.4), and the OR for leukaemia within 5 km of an NPP during 1980–2003 using this set of controls is 1.60 (95% CI = 1.01–2.53), which is marginally significant at the 5% level. However, the validity of this analysis does depend on the *a priori* assumption that an elevated risk in the <5 km zone is confined to leukaemia and does not extend to other cancers.

Table 4.4 Numbers of young children with leukaemia and other cancers, included in the KiKK study for all NPPs for the period 1980–2003 by distance zone

	Number of cases			
Cancer group	**<5 km from an NPP**	**≥5 km from an NPP**	**Total**	**Percentage <5 km**
Leukaemias	37	556	593	6.2%
Other cancers	40	959	999	4.0%
Total cancers	77	1515	1592	4.8%

4.82 To properly interpret the KiKK study results for leukaemia among young children resident at the time of diagnosis within 5 km of an NPP during 1980–2003, it is necessary to take into account the previously known marked excess of childhood leukaemia near the Krümmel NPP, which occurred from 1990 onwards and which would have affected the periods 1991–1995 and 1996–2003. The unmatched categorical OR of 4.75 (95% CI = 1.48–15.21) is a measure of the influence of the Krümmel data for 1991–2003. The categorical ORs for all NPPs except Krümmel for 1991–1995 and 1996–2003 are raised, but are far from being statistically significant. However, the categorical OR for all NPPs during 1980–1990 is significantly raised (OR = 3.00, lower one-sided

95% CL = 1.54), and this is largely due to the OR for all NPPs except Krümmel, which is also significantly raised (OR = 2.78, lower one-sided 95% CL = 1.42), although it is of interest that the one case within 5 km of Krümmel during 1980–1990 that was diagnosed in 1990 (and marked the start of the Krümmel cluster) also has some influence on the all NPPs grouping during 1980–1990. Therefore, apart from the influence of the Krümmel excess from 1990 onwards, it is the OR for all other NPPs during 1980–1990 that is an important factor in producing the statistical association reported from the KiKK study.

4.83 An interesting comparison can be made between the categorical unmatched ORs for the three sub-periods for all NPPs, all NPPs except Krümmel and Krümmel alone, and the equivalent RRs, and this comparison is summarised in Table 4.5. It will be seen that the Krümmel excess is reflected in both the OR and RR for 1991–2003, but that neither the ORs nor the RRs for all NPPs except Krümmel during 1991–1995 and 1996–2003 are notable. However, the contrast between the OR and the RR for all NPPs during 1980–1990 is striking, and worthy of attention. It may be that the difference is a result of the precise measure of the distance between a residence and the nearest NPP in the case–control study as opposed to the distance between the nearest NPP and the centroid of the community of residence in the geographical study, but this is not clear. For example, the same number of cases (13) is included in the <5 km zones in both studies and it is not obvious why the controls are a better indicator of risk than the expected number of cases in the communities in which these cases are observed. Conversely, these 13 cases may not be the same in both studies, and the case–control approach may have revealed an unusual small-scale spatial distribution of cases that is not apparent in the community-based study.

Table 4.5 Comparison between the categorical unmatched ORs for the sub-periods for all NPPs, all NPPs except Krümmel, and Krümmel alone and the relative risk values

Time period	NPP grouping	Categorical unmatched $OR_{<5km}$ vs $OR_{\geq 5km}$ from the KiKK study data (95% CI)	Relative risk $SIR_{<5km}$ vs $SIR_{\geq 5km}$ (95% CI)
1980–2003	All plants	2.11 (1.37–3.24)	1.44 (0.99–2.04)
	All except Krümmel	1.93 (1.20–3.11)	1.22 (0.79–1.81)
	Krümmel	4.53 (1.57–13.01)	4.24 (1.65–9.70)
1980–1990	All plants	2.86 (1.32–6.17)	1.29 (0.68–2.26)
	All except Krümmel	2.79 (1.25–6.21)	1.29 (0.66–2.32)
	Krümmel	4.50 (0.25–79.83)	1.34 (0.03–9.64)
1991–1995	All plants	2.06 (0.90–4.68)	1.61 (0.72–3.19)
	All except Krümmel	1.79 (0.64–5.02)	1.00 (0.32–2.37)
	Krümmel	4.64 (0.91–23.48)	10.07 (1.99–46.8)
1996–2003	All plants	1.72 (0.88–3.38)	1.49 (0.76–2.68)
	All except Krümmel	1.49 (0.71–3.13)	1.26 (0.57–2.44)
	Krümmel	5.22 (0.91–30.11)	3.96 (0.71–15.0)
1991–2003	All plants	1.85 (1.10–3.11)	1.54 (0.94–2.40)
	All except Krümmel	1.58 (0.87–2.89)	1.15 (0.62–1.96)
	Krümmel	4.75 (1.48–15.21)	6.03 (2.10–15.5)

4.84 A potential explanation is that representative control selection is a particular problem in this earliest sub-period 1980–1990 (possibly acting in combination with an under-registration of cases that is geographically heterogeneous during the early years of the childhood cancer registry). Against this interpretation is the absence of a notably raised OR for all cancers other than leukaemia, which would be expected if control selection bias is an important factor in the KiKK study. However, it would be of value to know the OR for all cancers other than leukaemia for 1980–1990, and the equivalent SIR and RR values, to shed light on this potential explanation for the leukaemia OR in terms of the selection of an unrepresentative set of controls. Kinlen (2011) considered the similar childhood leukaemia numbers in the two methodological approaches taken for the German studies as 'pointing to a problem with the KiKK study controls and the complexity of the selection process'.

4.85 Kaatsch et al (2008a) considered that the case–control approach of the KiKK study was preferable to the previous geographical studies because the distance of a residence from an NPP could be determined for each individual in the study. However, the use of a function of the reciprocal of the distance of the residence at the time of diagnosis from the nearest NPP as a surrogate for the relevant radiation dose received by a child is problematical. It is apparent from the SSK report that discharges from NPPs vary between sites and that the level of discharge tends to be higher in the earlier years of the KiKK study, and the simple distance measure cannot be expected to account for this (SSK, 2008). Moreover, the overall dose of radiation received by a child will be much more dependent on the source of food – a child eating local foodstuffs will ingest more discharged radionuclides than a child consuming food from a supermarket. Further, the analysis conducted in the KiKK study does not consider the length of time lived at the residence at the time of diagnosis or the locations of previous residences. Individual dose reconstruction was undertaken in the Northern Germany Leukaemia and Lymphoma (NLL) study to deal with such points (Hoffmann et al, 2003). It was intended that the KiKK study should address at least some of these issues through the questionnaire survey, but this had to be abandoned due to low and biased response. It is unclear just how a more sophisticated approach to dose estimation would affect the results. The KiKK study authors recognised the limitations of the distance measures as a surrogate for dose, and did not interpret the findings in terms of radiation exposure.

4.86 If the statistical association found in the KiKK study is not a result of bias (or chance), then an explanation in terms of factors other than exposure to ionising radiation is plausible. An examination of the possible influence of confounding factors had to be abandoned because the data collected from the questionnaire survey were unrepresentative of the eligible study subjects in terms of distance from an NPP.

4.87 The analysis described in Annex 6B of this report is indicative of a significant effect of demographic factors on the risk of leukaemia in young children; further analyses are described in our eleventh report (COMARE, 2006). It is not possible to say how much effect these factors might have on areas near German NPPs without information about their demographics and associated factors. From the analyses of Darby and Read summarised in Table 4.2, however, it is apparent that urban/rural status may be an important determinant of the risk of childhood leukaemia and it is likely that this is related to socio-economic status as well. If patterns of infection are important in determining the risk of childhood leukaemia then it is credible that a large industrial facility (such as an NPP) sited in a predominantly rural locality could produce an unusual network of contacts, which generates the relevant infective patterns that increase the risk of childhood leukaemia.

Summary

4.88 The KiKK study was an ambitious case–control study of the risk of cancer among young children living near NPPs in Germany over an extended period of 24 years. It was conducted in the wake of public concern in Germany over the risk of childhood cancer, in particular childhood leukaemia, that had arisen from earlier geographical studies and from the occurrence of the notable excess of childhood leukaemia incidence near the Krümmel NPP in northern Germany. Unfortunately, the interview component of the KiKK study, designed to assess the possible influence of confounding in the study, effectively had to be abandoned owing to poor and selective participation in the questionnaire survey. The essence of the findings of the KiKK study is the positive statistical association between the risk of leukaemia in a young child (under 5 years of age) and the nearness of the residence of the child to an NPP in an area within 5 km of the site. Excess radiation exposures to the general public as a consequence of living near NPPs in Germany are likely to be a factor of 1,000–100,000 times lower than those from background radiation and are unlikely to be the cause of this raised risk. The increased risk reported in the KiKK study is heavily influenced by the same cases identified in earlier German investigations (covering the time periods 1980–1990 and 1991–1995) in suggesting a raised risk of childhood leukaemia at ages up to 5 years within 5 km of the nearest NPP.

4.89 Previous evidence for a general elevation of the risk of leukaemia among young children living near nuclear installations in Germany has been weak. The original geographical study of Michaelis et al (1992) found a significantly raised incidence in areas around nuclear installations relative to control areas during 1980–1990, but these authors concluded that this raised relative risk was principally due to an unusually low SIR in the control areas, the SIR in installation areas being unremarkable. A follow-up geographical study by Kaatsch et al (1998) did not confirm this significantly elevated relative risk around the grouped German nuclear installations during 1991–1995, but did find a significantly raised incidence rate around the Krümmel NPP that was influencing the overall results; in the absence of the Krümmel data the incidence rate around nuclear installations was at expected levels. The Krümmel excess is striking and there is little doubt that it represents one of the more noteworthy findings of raised levels of childhood leukaemia incidence around nuclear installations. It is important, therefore, to assess the results of the KiKK study in the light of the existence of the Krümmel excess.

4.90 The Krümmel excess began in 1990. Table 4.3 shows the influence of the Krümmel excess upon the KiKK study results for the sub-periods 1991–1995 and 1996–2003, and the evidence of an excess risk of childhood leukaemia around NPPs in Germany during these two sub-periods in the absence of the Krümmel data is only weak. Of note are the KiKK case–control study findings for 1980–1990, when Krümmel had little impact upon the overall results and the odds ratio of 2.78 for the group of all NPPs except Krümmel is statistically significant. Indeed, the odds ratios are highest for this earliest sub-period. What is puzzling is the weakness of the evidence from the SIR values for this earliest sub-period for a raised risk of leukaemia, given the magnitude and statistical significance of the OR from the case–control study: the SIR values are unremarkable and contrast starkly with the OR values. It is of note in this respect that the SIR value for Krümmel during 1991–2003 indicates strongly the existence of the Krümmel cluster of cases, reflecting the strikingly raised OR for Krümmel during this period.

4.91 Increases in incidence rates in different time periods have also been seen in other countries and are unlikely to be specific to areas near NPPs. These increases may or may not be an artefact of registration or of altered diagnostic classification, and so may or may not represent a change in some unknown risk

factor. Whether these unknown factors are truly important in the aetiology of childhood leukaemia remains to be seen, but the analysis of the geographical distribution of childhood leukaemia throughout Great Britain presented in our eleventh report (COMARE, 2006) suggests that important background risk factors need to be taken into account when assessing the risk in any particular area. In this respect, the growing evidence for the role of infections in the risk of childhood leukaemia is of note.

4.92 Two possibilities present themselves for the disparity in risk estimates for the earliest sub-period 1980–1990 as determined by the case–control and geographical approaches: either the precise individual distance measures available to the case–control study reveal a risk that is not apparent in the geographical studies, or it is indicative of some problem with the case–control approach, potentially in the selection of representative controls, particularly in this earliest sub-period. It is difficult to understand why the pronounced risk indicated by the case–control study for this earliest sub-period should not manifest itself to a noticeable extent in the geographical studies; the number of cases included in the case–control study and the equivalent geographical study for the inner 5 km zone is the same (13), so presuming the affected children are much the same in the two studies, it would be expected that the geographical study would point to the raised risk indicated by the case–control study.

4.93 If the OR and SIR/RR values for this earliest sub-period are reasonably accurate then it would suggest that the affected children in the inner 5 km zone live closer to the NPPs than would be expected from the spatial distribution of the childhood populations of the communities in which they live (as given by the location of residences of the controls). If this is so, it is surprising that this has not been detected previously given the intense interest in the subject; but the difference in distance may not be especially great and still be detected by the case–control approach. This raises another interpretational point: if the difference between average case and control distances in the inner 5 km zone is small (as indicated by Spix et al, 2008), could the raised OR arising from this difference reasonably be attributed to an increase in radiation dose due to the difference in distance?

4.94 On the other hand, if control selection bias is the reason for the difference between the OR and SIR/RR values for this earliest sub-period, it would be expected that the problem would be manifest for cancers other than leukaemia as well as for leukaemia. Further information is required to properly understand this apparent discrepancy between the findings of the case–control and geographical studies and this should be examined further.

CHAPTER 5

REVIEW OF META-ANALYSES OF STUDIES ON THE RISK OF LEUKAEMIA IN YOUNG PEOPLE LIVING IN THE VICINITY OF NUCLEAR INSTALLATIONS

Introduction

5.1 This chapter reviews the evidence for the risk of childhood leukaemia in the vicinity of nuclear power installations by examining recently published meta-analyses. The evidence is reviewed in the light of the assumptions, strengths and weaknesses of such studies.

Meta-analyses

5.2 A meta-analysis is a type of statistical analysis that combines or integrates the results of several independent research studies to produce a single estimate. This method is being used with increasing frequency in clinical medicine as an attempt to improve on traditional methods of narrative review by systematically aggregating information and quantifying its impact (Thacker, 1988). Combining data from several studies using a meta-analysis can increase statistical power, provide insight into the nature of relationships among variables, and permit the generalisation of results more rigorously than less quantitative review methods.

5.3 Meta-analyses of observational data (eg case–control, cohort and geographical studies) are becoming increasingly common. However, their use in observational studies can be controversial if the protocols, data collection methods, definition of diseases, exposures, etc, differ between the datasets being combined. Publication bias (ie bias arising from the under-reporting of null findings) may be another issue. Hence, the selection of studies to include in a meta-analysis and the analysis of pooled data from different sources should be undertaken with care.

5.4 Meta-analyses can be of two essentially different forms, according to the nature of the underlying model and the parameter being estimated. In the fixed effects case, an assumption is made that the summary statistic from each study is estimating the same unknown quantity λ, say, such as a relative risk. In most circumstances, this is quite unrealistic as the true risks will vary according to the conditions (eg the levels of any local radiation discharges), as well as differences resulting from study design, such as the age group or distance considered. It is therefore nearly always preferable to use a random effects model, in which it is supposed that each study has its own true but unknown risk, ρ, that is estimated by the corresponding statistic. It is supposed that these different ρ values themselves have a distribution of values with an overall mean, μ, and standard deviation, τ. The object is now to estimate the mean of this distribution, μ. Using the fixed effects model, of course, is equivalent to assuming that $\tau = 0$. It is possible to test whether $\tau > 0$ and, if so, it can be said that there is (significant) heterogeneity in the data. The effect of using the random effects model is always to widen the confidence limits for μ, taking account of the extra variability measured by τ. To use a fixed effects model where there is appreciable heterogeneity can consequently give a very misleading impression of the precision of the estimate.

5.5 With count data, such as are often obtained from geographical studies, the normal method of applying a meta-analysis is to assume that the logarithm of the observed standardised incidence ratio (SIR) has a normal distribution, as this gives a more reliable approximation than using the untransformed SIR. There is a problem with small counts because log(0) is not a finite number and a common recourse is to replace 0 by 0.01; this adjustment has been used in the calculations given below. Although this introduces an arbitrary element into the calculations, using other small additions makes rather little difference; moreover, using a method based on a generalised linear model for the count data gives similar results.

5.6 This chapter reviews two recent meta-analyses of childhood leukaemia near NPPs – one by Baker and Hoel (2007) and the other a self-published report by Greiser (2009) prepared for the German Green Party.

Meta-analysis of standardized incidence and mortality rates of childhood leukaemia in proximity to nuclear facilities (Baker and Hoel, 2007)

5.7 A meta-analysis was conducted by Baker and Hoel (2007) from 17 published studies covering 136 nuclear sites in eight countries (Great Britain, Canada, France, the former East and West Germany, Spain, Japan and the USA) on the relationship between the risk of childhood leukaemia and proximity to nuclear facilities. Studies were selected for eligibility on the basis of pre-defined criteria, including:

(i) being cohort studies identifying individual nuclear sites;

(ii) considering both standardised incidence ratio (SIR) and standardised mortality ratio (SMR) estimates, with separate analyses for each;

(iii) the cases analysed were limited to leukaemias and excluded studies that did not distinguish leukaemia from lymphoma. This had the effect of excluding all comprehensive analyses of the British data.

5.8 The data were stratified according to endpoint (whether incidence or mortality), age group and distance considered; separate meta-analyses were reported for each stratum. Out of 37 individual studies, 17 were identified as appropriate for inclusion and data for the individual sites from these studies were examined in the respective meta-analyses. Within each stratum, a single combined estimate was calculated for incidence and mortality of leukaemia using both the fixed effects and random effects models. Heterogeneity between site results was tested using a chi-square test for homogeneity (Cochran, 1952) and a P-value less than 0.05 was considered to indicate statistical significance. Forest plots were used for each site's SIR or SMR with the corresponding 95% CIs. The authors also considered funnel plots for evidence of publication bias, but these were not published.

5.9 The study reported the results of the meta-analyses for each of the eight strata considered. For the stratum most relevant to the KiKK study findings (incidence for ages 0–9 years in zones less than 16 km), the overall estimate of relative risk using the random effects model was 1.22 (95% CI = 1.05–1.41). However, the authors noted that this result was influenced by large estimates at two sites that are not NPPs (Aldermaston and Amersham), which they saw as contributing to the heterogeneity, although they did not report significant heterogeneity in any of the strata. Excluding these sites reduced the overall estimate to 1.14 (95% CI = 0.98–1.33), so that without these two sites the apparent increase in risk was not significant. The authors concluded that, although an excess risk for childhood leukaemia around NPPs was demonstrated,

the study does not support a hypothesis in which the effect was related to radiation exposure.

5.10 The selection criteria of this study were criticised by Spix and Blettner (2009), who identified a number of limitations and flaws in this meta-analysis. The main concern was the general problem of summarising the heterogeneous data being combined. These included the different age groups (0–9 years or 0–25 years), the different types of nuclear facilities (NPPs and other nuclear sites) and the different zone definitions (<10 km or county). Furthermore, a number of specific problems were also identified: there was no explanation or discussion of the selection of 17 out of 37 individual studies; there was a selection bias resulting from the exclusion of sites with zero observed cases or deaths; and a methodological problem was identified, in that the forest plots showed CIs on a logarithmic scale that were asymmetrical, contrary to expectation.

Leukaemia in children and young people in the vicinity of nuclear power stations in five countries. Meta-analyses and analyses (Greiser, 2009)

5.11 Using data from several countries, Greiser (2009) reported a significantly increased leukaemia incidence among children and young people living close to an NPP. The study used available data in the literature and from cancer registries, including the recent studies in Germany (Kaatsch et al, 2008a; Spix et al, 2008). Data from the vicinity of 80 NPPs from five countries (Germany, France, Great Britain, the USA and Canada) were included in the analysis.

5.12 The findings from each NPP from the five countries were pooled in a meta-analysis to provide a combined estimate of the relative risk of leukaemia. The incidence of leukaemia was reported to be increased by 19% (95% CI = 13%–25%) among children aged under 5 years. Among children aged under 15 years, the incidence was reported to be increased by 13% (95% CI = 10%–17%) relative to the corresponding national or regional average rate.

Issues regarding the calculation of overall measures of risk and their uncertainty

5.13 COMARE has reviewed this manuscript and has some concerns relating to the methodology used. As described below, the meta-analysis has not been applied appropriately and the conclusion that 'there are statistically significant increases in leukaemia risks in various age categories of children and young people living in the vicinity of a nuclear power station' is not borne out when appropriate methods are applied correctly. The author does not consider the heterogeneity in the different studies, which is considerably greater than that reported by Baker and Hoel (2007). As the paper included the data from all the sites analysed, it has been possible for COMARE to re-analyse the data using the more appropriate random effects model.

5.14 The results of this re-analysis are given in Table 5.1, which shows the test statistics for heterogeneity. In all cases the studies show considerable heterogeneity in agreement with the observation that the CIs for the random effects model are substantially wider than those for the fixed effects model. The fixed effects intervals agree with those calculated by Greiser (2009), except for minor discrepancies that are due to the way the standard deviations were inferred from the CIs. The results from these meta-analyses were obtained using the 'meta' module in the 'R statistical package', open source software for statistical computing and graphics, which is freely available at www.r-project.org. To illustrate the heterogeneity between studies, CIs from the re-analysis for various age groups are shown in Table 5.1; the original data are taken from Table 4 in the report by Greiser (2009).

Table 5.1 Overall relative risk of leukaemia around NPPs, based on the values reported by Greiser (2009) and in the analysis conducted here

		COMARE analysis				
				Test for heterogeneity in odds ratio between studies		
Age group (years)	**Greiser's results (95% CI)**	**Fixed effects (95% CI)**	**Random effects (95% CI)**	**Q-statistic**	**Degrees of freedom**	**P-value**
0–4	1.19 (1.13–1.25) *	1.18 (1.12–1.24) *	1.07 (0.92–1.26)	245.42	36	<0.0001
5–9	1.14 (1.05–1.25) *	1.12 (1.03–1.21) *	0.96 (0.76–1.22)	101.98	18	<0.0001
10–14	1.24 (1.12–1.37) *	1.21 (1.10–1.32) *	1.01 (0.78–1.30)	94.62	18	<0.0001
0–14	1.13 (1.10–1.17) *	1.13 (1.10–1.17) *	0.98 (0.88–1.09)	530.29	72	<0.0001
15–19	1.20 (1.08–1.33) *	1.18 (1.07–1.29) *	0.93 (0.71–1.22)	93.59	18	<0.0001
20–24	1.22 (1.08–1.36) *	1.18 (1.07–1.31) *	0.92 (0.70–1.22)	77.74	18	<0.0001

* Relative risk is statistically significantly greater than 1 ($P < 0.0001$).

5.15 Figure 5.1 shows a forest plot with SIR estimates for children aged 0–4 years from 37 analyses (mostly representing different parts of the USA). The black squares represent the SIRs of the individual estimates with 95% CIs (horizontal lines). The size of each square corresponds to the weight of the study in the meta-analysis. The solid vertical line corresponds to no effect (SIR = 1.0). The overall effect (calculated as a weighted average of the individual SIRs) is indicated and CIs for the two models are represented by lozenges. The lozenge estimate for the fixed effects model (black) does not touch the line of no effect, indicating that the estimate obtained was statistically significant (SIR = 1.18, 95% CI = 1.12–1.24, $P < 0.001$). However, the lozenge (grey) for the random effects model was found to contain the line of no effect (SIR = 1.07, 95% CI = 0.92–1.26) and so is not statistically significant ($P = 0.38$). It is clear in Figure 5.1 that the meta-analysis is dominated by the studies in the USA, which are assigned about 84% of the weight in the combined effect under the fixed effects model, with the remaining studies being assigned about 1% for Germany, 8% for France, 3% for Great Britain and 4% for Canada. In contrast, under the random effects model, the weight for the USA is reduced to 70% and increased for other countries to about 3%, 4%, 17% and 6% for Germany, France, Great Britain and Canada, respectively.

5.16 The meta-analysis is influenced by four studies for which the estimates are much lower than expected. There is no obvious explanation for this and it is accordingly clear that the fixed effects assumption – that all studies estimate the same parameter – cannot possibly be sustained. It also casts serious doubts on the value of other estimates used in the calculation.

5.17 COMARE has also identified some specific problems in Greiser's study. The rationale for selecting these countries (Germany, France, Great Britain, USA and Canada) and omitting other countries where studies have also been conducted (eg Japan) was not explained. Rather than relying simply upon the mortality data used by Jablon et al (1990) in their analysis of US nuclear installations,

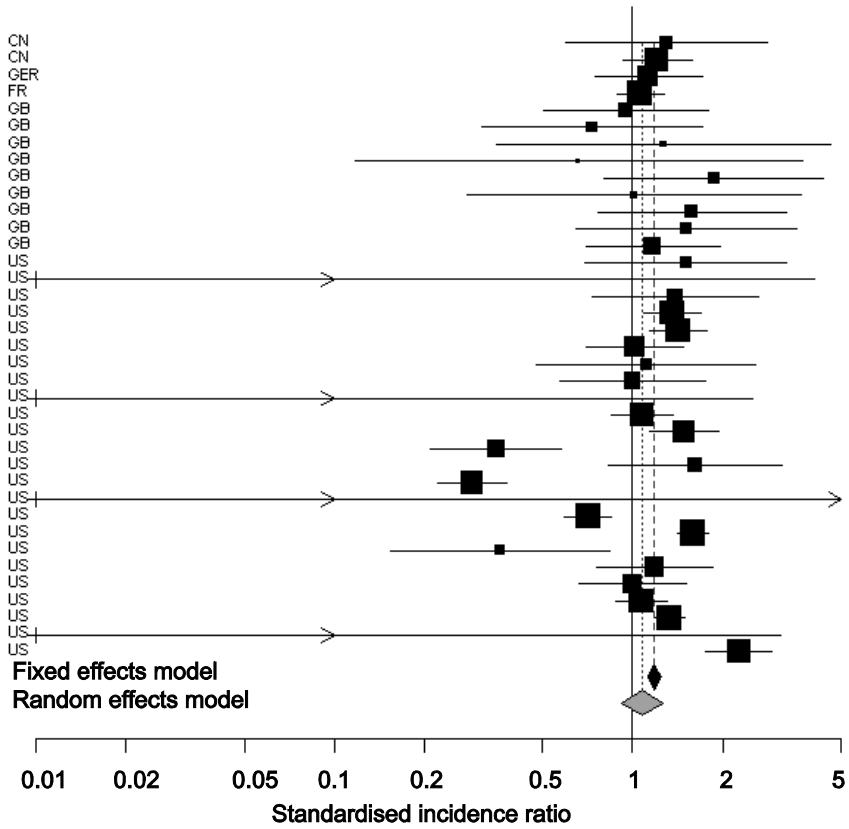

Figure 5.1 Forest plot of SIRs from individual estimates for children aged 0–4 years (CN, Canada; GER, Germany; FR, France; GB, Great Britain; US, United States of America). It should be noted that the SIRs with 95% CIs are drawn on a logarithmic scale

Greiser (2009) obtained cancer incidence data from the Surveillance, Epidemiology and End Results (SEER) Program (1973–2006), from cancer registries of Illinois (1987–2006), and from evaluations of two other cancer registries (Pennsylvania and Florida). However, the author did not specify how the comparisons of childhood leukaemia incidence rates were made, or how many cases were in the comparison groups.

5.18 The key problems with the analysis relate to the lack of information about the rationale for selecting the areas to be studied and the way in which leukaemia rates would be compared, together with the failure to take account of heterogeneity in the findings and to understand why these differences may have arisen. On this basis, COMARE considers that the study is largely uninformative and does not permit conclusions about the risk of childhood leukaemia near nuclear facilities.

5.19 The study by Greiser was also considered in a paper prepared for a special issue of *Jahrbücher für Nationalökonomie und Statistik* and kindly provided by its authors (Krämer and Arminger, 2010). The paper questions the selection of studies included in the analysis by Greiser. It was noted that some studies that determined no higher incidence of cancer around NPPs than elsewhere were not considered, whereas – with the selected studies – judicious adjustment of the parameters analysed, such as the time period studied, the type of cancer and the distance from the NPPs could permit 'significant' results to be established. The paper also refers to the practice of 'publication bias', where research yielding non-significant results may have less probability of being published than that reporting significant results.

Summary

5.20 Although meta-analyses would seem to be a powerful way of integrating the evidence from a large number of smaller studies, methodological differences severely limit their usefulness in practice.

5.21 There are concerns with the treatment of heterogeneity and the selection criteria used in both studies reviewed. The meta-analysis of Baker and Hoel (2007) did not demonstrate inter-study variability, but this was largely because it was dominated in the most relevant stratum (SIRs for children under 10 years within 16 km) by similar estimates from two British plants (Aldermaston and Amersham) that are not NPPs. The meta-analysis of Greiser (2009) suffers from major problems, including the inappropriate treatment of heterogeneity. The collection of data used in analyses and the selection of parameters can influence the results obtained. The relevance of these studies to nuclear power generation is therefore severely constrained.

CHAPTER 6

GEOGRAPHICAL ANALYSIS OF BRITISH CHILDHOOD LEUKAEMIA DATA

Introduction

6.1 Following publication of the results of the KiKK study on childhood leukaemia, a review of the evidence in Great Britain was undertaken and presented at the ICNIRP/WHO/BfS International Workshop on Risk Factors for Childhood Leukaemia in Berlin in May 2008*. For reasons discussed later, in paragraph 6.32, the methodology available in Great Britain was inevitably different from that used in Germany. Specifically, studies of British data employ a 'geographical analysis', in which disease incidence is calculated in relation to proximity to a source of risk; the method achieves a comparison with the population distribution using census data. This methodology is in contrast to that of the case–control analysis in the German study, in which individual cases are compared with population controls.

6.2 Previous geographical analyses of British data have been carried out on varying bases for over 25 years. In 1984 Baron investigated cancer mortality around nuclear facilities in England and Wales (Baron, 1984). The first comprehensive analysis of childhood cancer incidence (as opposed to mortality) around all the nuclear installations in England and Wales was described in 1994 by Bithell et al (1994) using data from the National Registry of Childhood Tumours (NRCT), which is maintained in Oxford by the Childhood Cancer Research Group (CCRG); an update was published in our tenth report (COMARE, 2005). Each of these analyses considered all cases of leukaemia and non-Hodgkin lymphoma (collectively referred to as LNHL) in children under 15 years of age, resident within a 25 km radius of each particular installation, and found no evidence of an excess in the number of cases within 25 km of any NPP. The KiKK study, as previously stated, found a raised incidence in young children (under 5 years of age) living within 5 km of any NPP. It was therefore decided to re-analyse the British data looking at incidence rates more closely aligned to the German study. The results of this study were published in 2008 (Bithell et al, 2008), and should be read in conjunction with a later paper (Bithell et al, 2010).

6.3 To correspond as closely as possible to the parameters of the German study, the British analysis deliberately omitted any adjustment of the data to incorporate known or suspected associations with demographic variables, such as had been done in earlier British studies. This approach was thought to provide the best comparison with which to answer the question of whether the British experience was different from the German one. In summary, the study found no significant evidence that there is a raised risk around NPPs in Great Britain, although the incidence was slightly raised within the 5 km circle. On the other hand, the difference between the risk estimates in the two studies was not statistically significant because of the considerable sampling errors in each. For the current analysis the question considered is whether there is independent evidence of a raised incidence among young British children and for this it

* http://www.icnirp.de/WChildhoodLeukemia.htm (accessed December 2010).

seemed best to specify the primary analysis following arguments used in the specification of previous studies.

6.4 Within this broad objective, there were many parameters of the analysis to be decided upon. Although it was not expected that differing choices of these parameters would make large differences to the results, it was felt necessary to focus on a pre-determined analysis to reduce the possibility of selection bias. Nevertheless, it is recognised that results should be available for scrutiny from various angles. The KiKK Review Subgroup of COMARE therefore identified a particular analysis as 'primary' (the agreed parameters of the analysis are detailed in paragraphs 6.5–6.14 below) and all other results presented in this report should be seen as subsidiary and not intended for purposes of formal inference.

Methods

6.5 The Subgroup discussed and decided on the methodology for this analysis as follows.

Cases included

6.6 The most recent analysis published considered cases in children under 5 years of age registered between 1969 and 2004 (Bithell et al, 2008, 2010). It was decided to use the same time period and age range for the current analysis, since any significant amount of later information would have entailed a delay in carrying out the analysis. Later years are also becoming increasingly difficult to analyse satisfactorily because of the ways in which recent census data are made available.

6.7 In line with the precept that the study should focus on the best possible scientific judgement rather than making the closest possible comparison with the KiKK study, it was decided to choose leukaemia and non-Hodgkin lymphoma cases (LNHL) for the primary analysis, as in our tenth report (COMARE, 2005). The reason for including non-Hodgkin lymphoma (NHL) cases is reviewed in Annex 6A, with a discussion of other subgroups that have been included and the resolution of the discontinuity between coding systems used by the NRCT and the German Childhood Cancer Registry. Overall, 8838 cases of LNHL (4968 males and 3915 females) registered in the NRCT between 1969 and 2004 entered the present analysis and, of these, 430 were registered at addresses in wards located within 25 km of an NPP. Throughout the analyses, males and females have been considered together.

Calculation of expectations

6.8 As with the previous systematic analyses of NRCT data, the observed units were counts in the electoral wards in England and Wales and roughly equivalent postcode zones in Scotland. Despite the rather different administrative derivations of these units, they are referred to generically as 'wards'. Unfortunately, the wards in England and Wales may change boundaries at successive censuses and this makes it difficult to perform comparisons over time. It was therefore decided to use 1981 ward boundaries, for which algorithms are available that relate them to 1971 and 1991 wards. These systems are not available for the 2001 census wards and therefore addresses were assigned to the 1981 ward with the nearest population centroid where necessary. Altogether there were 10,444 wards in the whole of Britain, ie in England, Wales and Scotland. Each count is associated with an 'expectation', which was obtained by a process similar to internal standardisation (see Bithell et al, 1995). In essence, each expectation is determined by using the overall rate for Britain (as observed in the dataset analysed) and applying it to the number of children aged 0–4 years in each ward.

6.9 It was decided to adjust these expectations for three demographic variables measured for each ward, namely the socioeconomic status (as measured

by the Carstairs index of deprivation in the area – Morris and Carstairs, 1991); the population density (the total population in the ward divided by its area) and the urban/rural status. These variables are the same as those used in our eleventh report (COMARE, 2006). The standardisation was performed by fitting a Poisson regression model as described in Annex 6B, the fitted values in this model providing the adjusted expectations. Further details of the calculation of the expectations are also given in Annex 6B.

6.10 The analysis by Bithell et al (2008) using this dataset was previously criticised for not considering population density as a possible confounder in the regression analysis (Körblein and Fairlie, 2010), a point that was addressed in the authors' response (Bithell et al, 2010). The adjustments described above for the analysis in this report demonstrate continued consideration of this issue.

Method of analysis

6.11 Analyses of NRCT data prior to 2008 have examined each nuclear installation in Britain separately (including installations with a primary function other than electricity generation). The numbers of cases around some plants were quite small for such separate analyses and it would have been difficult to obtain consistently coherent results from a statistical model relating incidence to distance. For this reason the methodology in these studies relied upon a class of non-parametric tests, the Linear Risk Score (LRS) tests, which make very few assumptions about the distribution of the cases and from which reliable significance test results can easily be obtained. When interest is focused on smaller distances and children under 5 years of age the problem of small numbers increases and for the current analysis – as with the post-KiKK analysis (Bithell et al, 2008) – all 13 sites were analysed as one, defining proximity in terms of distance to the nearest NPP. The reference circle was maintained at 25 km and, in this way, the analysis had sufficient cases to model risk as a function of proximity using a Poisson regression. This is the equivalent of the logistic regression used in the KiKK study for the case–control data and was chosen as the primary analysis for inferential purposes. The use of this model allows the estimation of a risk coefficient for comparison with that reported in the KiKK study. Although using the 25 km circle does not focus closely on the nearest 5 km circle, it should be expected to give more weight to any excess at small distances. Moreover, it must be recalled that there is no *a priori* scientific reason for supposing that any risk is of short range, still less that there should be a cut-off at 5 or 10 km.

Nuclear power plants included

6.12 The 13 NPP sites included in the analysis, together with the dates of commissioning and decommissioning of the respective reactors, are detailed in Table 6.1. Calder Hall, on the Sellafield site, has been excluded for the following reasons:

(i) The observation of an excess of childhood leukaemia near Sellafield was the 'hypothesis-generating' observation and good scientific practice proceeds by attempting to test hypotheses on independent sets of data.

(ii) Power generation has always been an incidental part of the activities on the Sellafield site, which have included nuclear operations (eg reprocessing) that release considerably more radioactivity into the environment than Calder Hall.

(iii) The well-known excess of childhood leukaemia cases in the village of Seascale adjacent to the Sellafield site would have an undue influence on the overall results, and distort the findings for the group of NPPs.

Table 6.1 NPPs in Great Britain, with their dates of operation

Location	Date of commission	Date generating ceased	Number of wards within 25 km
Berkeley	1962	1989	135
Bradwell	1962	2002	105
Chapelcross	1959	2004	33
Dungeness A	1965	2006	37
Dungeness B	1985	–	
Hartlepool	1983	–	137
Heysham 1	1983	–	97
Heysham 2	1989	–	
Hinkley Point A	1965	1999	80
Hinkley Point B	1976	–	
Hunterston A	1964	1990	58
Hunterston B	1976	–	
Oldbury	1967	–	150
Sizewell A	1966	2006	32
Sizewell B	1995	-	
Torness	1988	–	11
Trawsfynydd	1965	1993	27
Wylfa	1971	–	33

6.13 It is unfortunate that some commentators have seen the exclusion of Calder Hall, and therefore of Sellafield, in previous analyses as an attempt to minimise any apparent excess found in the data (Körblein and Fairlie, 2010). The reality, however, is that – had the data from this site been included – the results would certainly have yielded a higher estimate of risk, but it would have been entirely unclear what implications this had for purpose-built power-generating plants. The Sellafield and Dounreay sites are the subject of ongoing studies initiated by COMARE as a result of recommendation 5 of the eleventh report (COMARE, 2006) and are intended to form the basis of the fifteenth report.

6.14 Had Calder Hall, and therefore Sellafield, been included then it could reasonably be argued that other sites with a principal function that was not electricity generation but which possessed power reactors (eg Winfrith) should also be included. This would lead to a confused picture as far as nuclear power plants are concerned.

6.15 A similar exclusion approach was taken in the analysis by Evrard et al of nuclear sites in France, with the exclusion of Tricastin from the category of NPPs, due to its close proximity to Pierrelatte, a fuel conversion and fuel enrichment plant (Evrard et al, 2006). The two plants were considered as a single site for the analysis, separate from the NPPs. Similarly, White-Koning et al (2004) did not include Marcoule (an installation with a primary function other than electricity generation) in the group of NPPs, although, as with Sellafield, power reactors were present on the site.

6.16 Table 6.3 below reports the numbers of cases of LNHL within the 5, 10 and 25 km circles around any NPP, with their expectations, but these data should be regarded as exploratory and for general insight rather than for formal testing. It should be remembered that the Poisson regression was selected as the primary analysis and the significance of comparisons involving these counts is subject to this strong qualification. The regression analysis is repeated below for cases over a 10 km circle in view of the possibility that the larger circle has appreciably diluted any risk at short distances. Finally, for comparison with the analyses in our tenth report (COMARE, 2005), an LRS test using the reciprocal of distance as a measure of risk was carried out, with results given below.

Covariates employed

6.17 As discussed above, the expectations calculated adjust for population density, urban/rural status and Carstairs index. This inevitably changes the expectations in the simple descriptive analyses, but it also affects the Poisson regression, since the adjusted expectations are used in the model as an offset (see Annex 6B, paragraph 6B.1). A consequence of using the adjusted expectations is that the demographic variables should not be expected to make significant contributions to the regression. Accordingly they are not fitted in the analysis; the only explanatory variable is the proximity to the nearest NPP (see below). Taking account of the demographic associations in this way has the advantage that the adjustment uses information from the whole of Great Britain, which should give a more reliable adjustment than simply fitting these variables in the model for the restricted dataset; it also permits the reporting of the adjusted expectations in Table 6.3.

Distance measure

6.18 The exposure risk near an NPP is represented in the Poisson regressions by proximity, defined as the reciprocal of the distance to the nearest NPP from the centroid (or geographical centre of population) of each ward in the analysis. The refinement referred to in Bithell et al (2010) of calculating an aggregate proximity by summing the contributions from each NPP within a given distance was not used in this analysis. This made little difference, since only two NPPs are closer together than 50 km; the refinement has the disadvantage of complicating the explanation of the results. Ideally, an exposure measure more closely related to any physical risk, such as environmental radiation levels, would be used but, since there are few data on internal and external doses at the level of detail required, proximity has to serve as the best surrogate.

Results of the primary analysis

6.19 As discussed above, the chosen primary analysis is a Poisson regression for wards within 25 km of the nearest NPP. The model assumes that each count in a given ward has the well-known Poisson distribution, appropriate to the occurrence of events happening independently at random – for example, for cases of diseases with no element of contagion. The distribution has only one parameter, namely its mean or 'expected' count; this would be well estimated by the ward expectations, e_i, in the absence of any risk due to the NPP. If there is a risk, the model supposes e_i to be multiplied by a relative risk (RR), ρ_i, which is modelled as $\rho_i = \exp(\mu + \beta/x_i)$, where x_i is the distance to the nearest NPP, β is a risk coefficient determining the extra risk per unit of proximity (in km^{-1}) and μ is an 'intercept' determining the average risk in the 827 wards near an NPP, to the extent that this is different from the national average.

6.20 The maximum likelihood estimate (MLE) of β from the fitted model is 0.068 ± 0.940, giving a 95% CI for β of –1.77 to 1.91. Table 6.2 gives the estimated risks (relative to an indefinitely large distance) interpolated at 5, 10 and 25 km, with the 95% CIs.

6.21 The primary analysis, chosen beforehand, reveals no significant evidence of an association between risk and proximity to an NPP in the British data. This result should be taken into account when considering the further analyses below.

Table 6.2 Relative risk for LNHL cases (aged 0–4 years) due to proximity to an NPP at varying distances, as estimated from the Poisson regression model for 827 wards within 25 km

Distance (km)	Relative risk (ρ) (with 95% CI)
5	1.014 (0.70–1.47)
10	1.007 (0.84–1.21)
25	1.003 (0.93–1.08)

Secondary analyses

Numbers of cases near NPPs

6.22 Table 6.3 shows the numbers of cases of LNHL observed and expected in wards that are within 5, 10 or 25 km of an NPP in Great Britain, together with the SIRs and their 95% CIs. Similar counts for other diagnostic categories are shown in Annex 6A, Table 6A.2.

6.23 The SIRs are shown in Table 6.3 with the 95% CIs constructed using the 'exact' method, based on the Poisson distribution. No truly exact method exists for constructing such intervals; these are conservative, in the sense that the probability is at least 95% that the true value of the parameter should be contained in such an interval. As the intervals all contain the null value of unity (indicative of no excess risk), no SIR is significantly different from one, using this exact test. There is no scientific reason to select 5 km rather than any other radius and it is not justifiable to test formally the difference between the first and the next 5 km, this difference being enhanced in this study by an abnormally low incidence in the latter; it therefore seems hard to attribute this difference to anything other than chance.

Table 6.3 Observed and expected LNHL cases (aged 0–4 years) in wards within a given distance of an NPP in Great Britain

Distance (km)	Number of wards	Observed	Expected	Obs/Exp (SIR) (with 95% CI)
<5	34	20	16.35	1.22 (0.75–1.89)
<10	138	61	71.16	0.86 (0.66–1.10)
<25	827	430	463.93	0.93 (0.84–1.02)

Poisson regression within a 10 km circle

6.24 As discussed above, the Poisson regression was repeated using only those wards that lie within 10 km of an NPP. The resulting coefficient is 1.59 ± 1.43, giving a 95% CI of –1.21 to 4.40. This is clearly a larger estimate than in the 25 km analysis, but does not achieve statistical significance. Table 6.4 shows the interpolated RRs, analogous to Table 6.2, but in an analysis in which only wards within 10 km of an NPP are considered. Again, this is more suggestive of a slight positive risk at 5 and 10 km, but the estimates are not significantly different from the null value of one.

Table 6.4 Relative risk for LNHL cases (aged 0–4 years) due to proximity to an NPP at varying distances, as estimated from the Poisson regression model for 138 wards within 10 km

Distance (km)	Relative risk (ρ) (with 95% CI)
5	1.376 (0.78–2.41)
10	1.173 (0.89–1.55)

LRS tests on ward data

6.25 As discussed above, our tenth report relied upon the use of the LRS test introduced by Bithell et al (1994). This class of tests permits the use of any score τ_i that might reflect the risk in ward i. It has the advantage that it is the most powerful test against the hypothesis that the relative risk is given by $\rho_i = \exp(\tau_i)$; this would permit the selection of this test if the true RRs in each ward, ρ_i, were known. Generally these are not known, but for certain 'canonical' tests – using as scores the reciprocal of distance or its rank – it is possible to obtain results that achieve high power amongst a wide range of alternative hypotheses. In our tenth report (COMARE, 2005), a small group of contending possible tests were evaluated separately for each NPP since, in practice, the best test depends on the population distribution as well as on the alternative hypothesis. The best of these tests was predominantly an LRS test based either on the reciprocal of distance or on the square root of distance rank, with little to choose between them. There is justification in using the reciprocal of ward distance as a score in this analysis. This accords with the risk score used in the regression analysis and could be expected to give similar results, though making fewer distributional assumptions. The test therefore serves as a robust alternative to the Poisson regression, in which the inferences are made using assumptions dependent on sample size.

6.26 The test is carried out by simulating new sets of counts from Poisson distributions with the corresponding e_i as means and recalculating the LRS statistic at each stage. In 10,000 such simulations 8,964 were greater than the value observed for the actual data, yielding an estimated one-sided P-value of 0.90. Thus, the test yields no evidence of an excess of LNHL related to distance within 25 km of an NPP.

Analysis of 'potential' or 'control' NPP sites

6.27 In line with suggestions in the literature, the incidence of LNHL near a number of 'potential' or 'control' sites in Great Britain has been examined; these are sites selected as possible locations for NPPs, but where no installation was constructed. The intention of the analysis is to see if there is any obvious tendency for sites typical of those where NPPs are located to experience a raised risk. For this, the analysis used the six sites selected for the same purpose in Bithell et al (1994), which were locations under consideration by the then Central Electricity Generating Board for future development of NPPs. An additional site, considered more recently, has been included where there is already a conventional dual-fuel power station; this was quite close to London and the 25 km circle therefore included a large population. A further proposal was situated in an isolated rural location; this turned out to have no ward centres within 25 km and was therefore not considered.

6.28 The regression coefficient in the regression analysis corresponding to the chosen primary analysis (see paragraphs 6.5–6.14) was 1.60 ± 0.82, giving a 95% CI of 0–3.20, on the margin of statistical significance at the 5% level. Table 6.5 shows the observed and expected numbers within 5, 10 and 25 km of any of the seven sites considered, with the corresponding SIRs and the 95% CIs.

Table 6.5 Observed and expected LNHL cases (aged 0–4 years) within a given distance of seven potential NPP sites

Distance (km)	Number of wards	Observed	Expected	Obs/Exp (SIR) (with 95% CI)
<5	22	26	15.12	1.72 (1.12–2.52)
<10	108	98	90.32	1.09 (0.88–1.32)
<25	575	492	496.6	0.99 (0.91–1.09)

6.29 The significant excess within 5 km is entirely due to one site, where 5 cases were observed in wards within a 5 km circle, compared with 1.23 expected, giving an SIR of 4.06 (95% CI = 1.32–9.48). This same excess was detected by the LRS test in the analysis reported in Bithell et al (1994). The site is rural and situated on the east coast in the North of England. No obvious explanation for the excess has been determined.

6.30 This striking excess may be due to chance, and the result serves as a reminder that statistically significant results will occur by chance and that this is a more likely explanation with small datasets, which inevitably have low power. However, the result could point to some feature of the sites chosen for NPPs that increases the risk of childhood leukaemia, as previously noted by Cook-Mozaffari et al (1989b) (see paragraph 3.6), although the nature of such a feature has yet to be identified.

Critique of the study

6.31 No study can show that there is no risk, of course, and it is instructive to consider ways in which a negative study may have failed to detect a genuine true risk.

Size of the study

6.32 The study is of a quite reasonable size and should therefore have enough power to detect any appreciable risk. If, for example, the risk in the wards within the first 5 km had been twice that in the population as a whole – a figure roughly in line with the KiKK study findings – this should have been detected with a probability of 0.90 in a one-sided exact test at the 5% level. It would seem, therefore, that a failure to find an important effect in this analysis is not due to an inadequate study size.

The risk variable

6.33 As cases are allocated to ward centroids in Great Britain, the study undoubtedly loses some power to detect a distance effect relative to one in which distance is measured precisely for each place of residence, as with the KiKK study. This has previously been commented on as a potential area for imprecision (Körblein and Fairlie, 2010). However, the importance of this lack of specificity is unclear, considering that no environmental risk factor has been detected, much less shown to be linearly associated with distance. Given that people are quite mobile in the area surrounding their homes, it may even be that the location of the centre of population is more important than that of the individual residence. Estimation of the populations in the geographical units also introduces an element of inaccuracy in our study, especially because of the long time period studied. It would undoubtedly be good to carry out studies on smaller time and space units, but resources currently available do not permit this.

Ascertainment of cases

6.34 A study may sometimes fail to detect a risk because of incomplete ascertainment of cases, but this would presuppose that there was a connection between the ascertainment and the risk variable. It seems implausible that the ascertainment of the NRCT – believed to be around 98% – should be related to proximity to an NPP.

Ascertainment of population comparison

6.35 The case distances are compared with distances obtained for the general population and this comparison is made on exactly the same basis for each, ie by locating the cases to the centre of the ward in which they reside. The comparison presupposes knowledge of the size of the population at risk and this undoubtedly introduces an element of inaccuracy that is hard to assess. But it seems unlikely that it would lead to a systematic bias in the distributions of distance involved.

Controlling for confounding variables

6.36 A study could fail to demonstrate an effect because of a failure to adjust for confounding variables, though in practice the latter seem more generally to increase an apparent association than to reduce it. A geographical analysis is undoubtedly limited in respect of the variables which it can control and such as are available must be imputed to all individuals in an area, as with the risk variable. The normal way of obtaining individual data is through a case–control study and this often introduces considerable possibilities for bias (see paragraphs 4.79–4.81).

Requirements for a case–control study in Great Britain

6.37 Geographical studies have often been adversely compared with case–control studies. It is true that exposure and other variables for which the study is controlled are imputed to individuals from the properties of the areas in which they reside. This is often referred to as resulting in the 'ecological fallacy', but it would be more accurate to say that it leads to a loss of power and a bias in risk estimates rather than that it invalidates a study. However, geographical studies have the major advantage of objectivity, whereas it is generally hard to find controls that are not subject to some possibility of bias, particularly when they involve interviews or when they come from an essentially different source from the cases. The nature of the record systems in Germany is quite different from that in Great Britain. It enabled the KiKK study team to use local population registers, maintained by the legal requirement to register a change of address. No such requirement exists in Great Britain and it is not possible to find a reliable equivalent register.

6.38 To carry out a study identical to that of the KiKK study team, therefore, would require the establishment of new linkages between different registers with attendant changes to regulations and/or legislation. Leaving aside funding issues, such a project could not have been carried out within the timeframe of this report.

Summary

6.39 A geographical analysis of British data has been carried out for leukaemia and non-Hodgkin lymphoma, the latter included on histological grounds (see Annex 6A, paragraph 6A.2). The results of the primary analysis – chosen beforehand for formal testing purposes – give no statistically significant evidence of an association between LNHL and proximity to an NPP in Great Britain. There is evidence of a very slightly and non-significantly raised incidence of ALL in the first 5 km, as has appeared in previous analyses (Bithell et al, 2008, 2010); however, no *a priori* reason for this comparison has been proposed. The results of the analysis of potential NPP sites demonstrate that 'positive' findings must be interpreted with caution.

6.40 A critique of the study examining five possible reasons for a negative finding suggests no significant failings except for a loss of power resulting from the nature of a geographical analysis. It is possible to conclude that, in spite of its limitations, the geographical analysis of data from the NRCT is indicative of an estimate of risk associated with proximity to an NPP that is extremely small, if not actually zero.

ANNEX 6A

SELECTION OF AND ANALYSES FOR OTHER CANCER GROUPS

Choice of cancers in the primary analysis

6A.1 Table 6A.1 shows the numbers of cases of different cancers in the NRCT for the years 1969–2004, with the numbers in wards within 25 km of an operating NPP, classified according to ICCC-3. This is the latest version of the International Classification of Childhood Cancer, a coding system specialised to childhood cancers and widely used internationally (Steliarova-Foucher et al, 2005). The ICCC-3 is itself derived from ICDO-3, a version of the International Classification of Diseases (ICD) that is specialised to oncology. Because previous NRCT analyses and the KiKK study were based on earlier coding systems, it was necessary to consider in detail exactly which subgroups should be considered for the primary analysis.

6A.2 The subgroups finally selected consisted of all cancers classified as leukaemias (Group I) or non-Hodgkin lymphomas (Group IIb), apart from Group Id 'myelodysplastic syndrome and other myeloproliferative diseases'. Group Id was excluded on the grounds that no equivalent cancers were included in previous analyses; indeed, the conditions in this group were not previously classified as malignant (Steliarova-Foucher et al, 2005). NHL, on the other hand, was included – as for the tenth COMARE report (COMARE, 2005) – because the distinction between some cases of NHL and lymphoid leukaemia is defined arbitrarily by infiltration of the bone marrow with more than 25% of lymphoblasts. Particularly for the earlier years considered, it is possible that some cases then classified as NHL would now be regarded as cases of ALL. For example, three cases of NHL in the vicinity of Dounreay were subsequently reclassified as lymphoid leukaemia (COMARE, 1988).

Table 6A.1 Numbers of cases of leukaemia and NHL in Great Britain (1969–2004), with numbers resident within 25 km of an operating NPP

		Number of cases				
ICCC-3	**Cancer group**	**Males**	**Females**	**Total**	**%**	**<25 km of an NPP**
Ia	Lymphoid leukaemias (LL)	3889	3050	6939	76.1	340
Ib	Acute myeloid leukaemias (AML)	569	535	1104	12.1	61
Ic	Chronic myeloprolific diseases (CMD)	65	41	106	1.2	2
Ie	Unspecified and other specified leukaemias	95	104	199	2.2	11
All leukaemias		*4618*	*3730*	*8348*	*91.5*	*414*
IIb	Non-Hodgkin lymphomas, except Burkitt lymphoma (NHL)	350	185	535	5.9	16
LNHL		*4968*	*3915*	*8883*	*97.4*	*430*
Id	Myelodysplastic syndrome and other myeloproliferative diseases (MDS)	154	86	240	2.6	13
Total		***5122***	***4001***	***9123***	***100***	***443***

Table 6A.2 Observed and expected numbers of cases within the wards at different distances of any NPP in Great Britain for different cancer groups

		Distance of any NPP					
		<5 km		<10 km		<25 km	
ICCC-3	Cancer group	Obs	Exp	Obs	Exp	Obs	Exp
Ia	Lymphoid leukaemias (LL)	19	12.97	49	55.96	340	364.75
Ib	Acute myeloid leukaemias (AML)	1	1.98	10	9.25	61	57.41
Ic	Chronic myeloprolific diseases (CMD)	0	0.15	0	0.71	2	5.14
Ie	Unspecified and other specified leukaemias	0	0.26	1	1.18	11	9.47
All leukaemias		*20*	*15.37*	*60*	*67.11*	*414*	*436.76*
IIb	Non-Hodgkin lymphomas, except Burkitt lymphoma (NHL)	0	0.97	1	4.06	16	27.18
LNHL		*20*	*16.34*	*61*	*71.16*	*430*	*463.93*

Numbers in different cancer groups near NPPs

6A.3 Table 6A.2 shows, for different cancer groupings, the numbers of cases within 5, 10 and 25 km of an NPP, together with their expectations. It is re-emphasised that these are intended for background information rather than for formal inferential purposes; in particular, they show how little difference is made when the rarer cancers are included. For example, there are no cases of NHL within 5 km of an NPP, although including them in the primary analysis has slightly increased the expectation. The deficit of NHL within the whole 25 km zone is almost certainly due to chance – the observed value of 16 is significantly low, with a two-sided P-value of 0.03.

Regression analyses for other cancer groups

6A.4 As a sensitivity analysis, and to facilitate comparison with other studies, the Poisson regression analyses were carried out as described in paragraphs 6.18 and 6.19 for different cancers and cancer groups, with the results shown in Table 6A.3. The standard errors on the coefficient β are in all cases greater than the absolute values of the estimates, indicating that for no combination of cancers in the regression is β close to statistical significance. The largest relative risk is observed at 5 km for the lymphoid leukaemias (LL) alone, but there is no evidence of a raised risk for AML as was found in the KiKK study. The lower estimate of β obtained with the inclusion of NHL is due to the under-representation of these cancers near NPPs, as discussed in paragraph 6A.3.

Table 6A.3 Results from the Poisson regression analyses for other cancer groups

				Relative risk		
ICCC-3	Cancer group	β-value	Standard error on β	at 5 km	at 10 km	at 25 km
Ia	Lymphoid leukaemias (LL)	0.55	1.00	1.12	1.06	1.02
Ib	Acute myeloid leukaemias (AML)	–0.27	2.60	0.95	0.97	0.99
All leukaemias		*0.26*	*0.94*	*1.05*	*1.03*	*1.01*
LNHL		*0.068*	*0.94*	*1.014*	*1.007*	*1.003*

ANNEX 6B

FURTHER DETAILS OF THE ANALYSES

Calculation of the expectations

6B.1 The calculation of the expectations for the wards considered was quite complicated and employed the following procedure, which was only slightly different from that outlined in Bithell et al (2008).

(i) Three separate datasets were constructed corresponding to the years 1969–2004, 1983–2004 and 1988–2004 because three NPPs were commissioned after 1969, the start date for the study. For each of these datasets, the numbers of cases in each 1981 electoral ward were tabulated from the NRCT files. No attempt was made to take account of the decommissioning of the plants, in part because of the possibility that any effect related to a plant could persist beyond decommissioning.

(ii) For each of the three datasets the child population (0–4 years) was determined for each of the censuses 1971, 1981 and 1991 in each of the 1981 wards. Populations for intermediate years were estimated by linear interpolation between the enclosing censuses. [Thus, for example, 1983 was estimated as (8 × the 1981 count + 2 × the 1991 count)/10.] Use of the 2001 census was not possible because of the difficulty of obtaining a correspondence with wards defined earlier; for the later years we therefore simply extrapolated the 1991 values.

(iii) Expected numbers were then calculated (for the 1969, 1983 and 1988 series separately) by fitting a Poisson regression that assumed that the mean for ward i with child population N_i is given by

$$N_i \times \exp(\mu + \alpha x_i + \beta y_i + \gamma z_i) \qquad (1)$$

where μ, α, β and γ are parameters and x_i, y_i and z_i are the demographic variables representing quintiles of population density, urban/rural status (a six-level classification published with census data) and social deprivation, the last measured by quintiles of the Carstairs index (Morris and Carstairs, 1991); each of these quantities relates to the 1981 wards. For each series, wards with no children in the population were excluded from the regressions. Taking the logarithm of equation 1 gives a linear model for the parameters together with a term equal to $\log N_i$, which is known as an offset.

(iv) For each of the 13 NPPs, files containing distances of all wards from each plant were constructed (using the published centroids of the wards). The minimum of these distances was determined for each ward and the series appropriate for the nearest plant was used to define the observed and expected numbers for the ward. Wards within 25 km of an NPP were then abstracted, giving a total of 827 wards altogether.

6B.2 The procedure described carried out three separate modelling processes to standardise the expectations for the three separate series of years. For the longest series of years, 1969–2004, and the LNHL data, the Poisson regression gave the analysis of deviance shown in Table 6B.1. The theory of the Poisson regression model assures us that each of the deviance terms in the second column

Table 6B.1 Analysis of deviance table for LNHL for the years 1969–2004

Source of variation	Deviance *	Number of degrees of freedom † (df)	P-value	Residual deviance	Residual df
Population density	15.7	4	0.0035	10440.7	10408
Urban/rural status	5.76	5	0.33	10434.9	10403
Socioeconomic status (Carstairs index)	39.8	4	$<10^{-7}$	10395.1	10399

* Deviance reduction from fitting each term in the order shown.
† For this component of the deviance.

of the table should – to a good degree of approximation – have a chi-square distribution with the corresponding number of degrees of freedom (df), provided that a model with only the preceding terms is correct; each row of the table thus provides a test of the importance of a new term, given the effects of those already fitted. As can be seen from the P-values in the fourth column, fitting population density shows a significant reduction in deviance, while urban/rural status produces little further reduction. These variables are associated, however, and fitting urban/rural status first on its own does show a significant association with leukaemia incidence ($\chi^2_5 = 17.9$ with 5 df, P = 0.0031), although now the effect of population density is not significant.

6B.3 Even allowing for these demographic variables, fitting the Carstairs index achieves a highly significant further reduction in deviance, indicating the importance of socioeconomic status as a determinant of leukaemia risk. The coefficients for these variables do not behave monotonically or coherently and the direction of the effect depends on which other factors are fitted. It seems clear that all three variables are associated with one another, but that socio-economic status is much the most important.

6B.4 The modelling process provides 'fitted values', which are effectively obtained by substituting estimates of the parameters into equation 1. These are then our best estimates e_i of the expected numbers of cases that we should observe in each ward and that are used for subsequent analyses. The goodness of fit of the model with all parameters fitted cannot immediately be judged from the residual deviance since this will not have a reliable chi-square distribution when the expectations are small. This deviance, D, is, however, equal to

$$2\sum_i \left(y_i \log(y_i / e_i) - y_i + e_i \right) \quad \text{(on the understanding that } 0 \times \log 0 = 0\text{)}$$

and we can test it to a good approximation by sampling new values for y_i from Poisson distributions with the corresponding e_i and recalculating the deviance each time. Carrying out this procedure 1000 times yielded 12 values of D that were larger than D_{obs}, which gives an estimated P-value of 0.012 and from which we conclude that there is some unexplained residual heterogeneity in the data, although, bearing in mind the large number of observations, this would not seem to be at a high level. These results are in line with previous findings, as discussed in the eleventh COMARE report (COMARE, 2006).

CHAPTER 7

OTHER FACTORS – CHILDHOOD LEUKAEMIA PATHOLOGY AND CANCER REGISTRATION

7.1 Childhood leukaemia is not a single, homogeneous disease (Greaves, 1993). Diagnosis is becoming more precise with morphology being accompanied by immunological, cytogenetic and molecular markers of disease. Subtypes of leukaemia can be defined through chromosomal translocations with the creation of fusion genes, deletion of individual genes or chromosomal segments, and duplication of sections or whole chromosomes. Both acute lymphoblastic leukaemia (ALL) and acute myeloid leukaemia (AML) have definable subtypes (Eden, 2010).

Causes of childhood leukaemia and potential relationships to leukaemia around nuclear sites

7.2 Cancer arises because of genetic damage. It is possible to delineate four distinct demographic populations with different expectations of cancer depending on environmental and inherited variables. The term 'oncodeme' has been suggested for these populations (Knudson, 1985). First, it is likely that for any kind of cancer there is a background rate of unrepaired mutations, which define a minimum incidence that cannot be reduced. Second, there are individuals who have inherited a predisposing mutation. Third, there are individuals with inherited defects of DNA repair. Finally, and most importantly in the context of this report, there is a variety of environmental agents, which can alter the host genome and hence increase the likelihood of acquiring an unrepaired mutation; it is possible that the majority of adults affected by cancer fall into this oncodeme.

7.3 Induction of adult cancers may involve prolonged exposure to an environmental agent (or agents) and accumulation of a number of genetic mutations before the malignant process is finally triggered. In children the possible timing of exposure is very much shorter, encompassing the periods *in utero* and after birth. However, since no new oocytes are formed after birth and maturation occurs during gestation, very early maternal exposure might also be important. In contrast, the effect of paternal exposures should be more independent of age at exposure, since spermatogenesis continues from puberty to old age. Thus prenatal exposures, both preconceptional and *in utero*, may be of relevance as well as any that occur during the period from birth to the time shortly before diagnosis.

7.4 Although the interval between the initial symptoms and diagnosis may be very brief, the malignant cell may have begun proliferation months or even years before the onset of symptoms. The time period of transition of a cell from normal to malignant remains unclear and is probably also very variable. In the case of acute lymphoblastic leukaemia (ALL), the peak age of onset is at around 3 years, again suggesting that prenatal environmental exposures may be of importance.

7.5 Since publication of the Independent Advisory Group report (Black, 1984), which investigated the possible increase in cancer in West Cumbria, there have been considerable advances in the classification of leukaemia so that it is now possible to discern a variety of subtypes on the basis of cytogenetic,

immunophenotypic and molecular genetic differences. There is emerging evidence that the subtypes may have differing aetiologies.

7.6 Immunophenotypic characterisation is based on the cell-surface expression of a variety of proteins, the antibodies to which are denoted by CD numbers. For example, CD10 was previously known as the common ALL antigen. Using this approach it is possible to determine the degree of maturation of the leukaemia cell along the normal differentiation pathway. This process is still of use in ascribing cell lineage, but early attempts to use it as a basis for prognosis have now largely been superseded by the use of cytogenetic or molecular genetic techniques.

7.7 Cytogenetic abnormalities are microscopically visible manifestations of DNA damage. The first leukaemia-type-specific abnormality to be described was the 'Philadelphia chromosome' in 1960 (Nowell and Hungerford, 1960), but since then a large number of specific cytogenetic abnormalities have been described. The advent of chromosome banding techniques (Seabright, 1971) enabled recognition of individual chromosomes and the characterisation of the Philadelphia chromosome as being a reciprocal translocation of genetic material between chromosomes 9 and 22; more recent observations include a wide range of translocations with varieties of partner chromosomes, as well as deletions and amplifications. The range of cytogenetic abnormalities now described may be used to classify and group subtypes of ALL and are also of prognostic significance (Moorman et al, 2010).

7.8 Molecular genetic techniques are capable of generating vast quantities of data, and part of the challenge of the new techniques has been to develop appropriate analytical methods. Typically it is possible to recognise common patterns of expression of a variety of leukaemia-related genes and to relate these patterns of expression to cytogenetic or immunophenotypic data, so enabling precise definition and recognition of subtypes of the disease.

7.9 Whilst useful in the classification of leukaemia and in understanding its genesis, the presence of a chromosome translocation or other abnormality gives no clue as to any precipitating factors. A variety of environmental factors that might lead to DNA damage have been identified, including a number of lifestyle factors, radiation and infection. In general, there are no data to support a role of lifestyle factors as important in the genesis of childhood leukaemia, although it is possible that some such factors might influence the role of infection – for example, by increasing exposure time. The factors exciting most interest have been radiation – ionising and non-ionising – and infection. That exposure to low doses of radiation *in utero* might be involved in the genesis of childhood malignancy was first documented in the Oxford Survey of Childhood Cancers during the late 1950s (Stewart et al, 1958), and many studies have confirmed the association between foetal exposure to X-rays and childhood leukaemia (Wakeford, 2008). The roles of gestational age at the time of exposure and dose are the subject of further debate, as is the potential role of paternal occupational exposure.

7.10 Preconceptional radiation exposure of fathers' sperm has been advanced as a possible mechanism to explain the apparent paternal dose-related increase in the risk of childhood leukaemia found in the West Cumbria case–control study by Gardner et al (1990). No excess of leukaemia has been identified, however, in the offspring of Japanese atomic bomb survivors, nor in the offspring of other British or Canadian nuclear workers (Draper, 2008). An American study of children of workers at three nuclear sites in the USA similarly did not provide any evidence of excess risk (Sever et al, 1997). The seventh COMARE report

concluded: ‘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’ (COMARE, 2002). Interestingly, and supporting the notion that environmental factors other than radiation should be examined, Gardner et al also found increased risk associated with workers in the iron and steel, farming and chemical industries (Gardner et al, 1990).

7.11 There is currently little evidence to support the notion of a role for non-ionising radiation.

7.12 Some infective agents undoubtedly cause specific cancers, eg HTLV-1 in adult-type T-cell leukaemia/lymphoma and Epstein Barr virus in Burkitt’s lymphoma. Such a simple relationship between agent and disease has not been demonstrated in the case of childhood leukaemia.

7.13 Nevertheless, the idea of an infective origin in childhood leukaemia is long standing, fostered in part by the associations noted above, and by reports of apparent clusters of childhood leukaemia. Kinlen has advanced the hypothesis that childhood leukaemia is a rare response to a common infection, and that unusual population mixing leads to the introduction of the relevant infectious agent to a pool of susceptible individuals, so increasing the risk of leukaemia in this group (Kinlen, 2011). It must be emphasised, though, that at this point no specific agent has been identified in childhood leukaemia.

7.14 However, nearly all examples of rural/urban population mixing within Great Britain over the past 70 years have been examined for evidence of an association with childhood leukaemia, and in a variety of situations there have been transient but significant excesses of childhood leukaemia. It is notable that 12 examples of population mixing were not associated with nuclear facilities. Of the five established childhood leukaemia excesses near nuclear sites, four are associated with significant population mixing. The fifth, near the Krümmel nuclear power plant in Germany, has not yet been investigated for the possible role of population mixing.

7.15 More recently, Greaves and colleagues (Gale et al, 1997) have shown – for example, by examination of postnatal blood samples such as Guthrie spots – that an initial, predisposing mutation (eg a chromosomal translocation) can occur *in utero*, presumably during rapid expansion of B-cell precursors in foetal bone marrow and liver. Since these abnormalities can be detected at a far higher frequency than that of overt leukaemia, there must be subsequent genetic events within clones of predisposed cells that occur postnatally, and which ultimately lead to the development of the clinically recognisable disease. The causes and timing of these events remain the subject of speculation.

7.16 Greaves has developed the delayed infection hypothesis (Greaves, 1988, 2006), which suggests that second mutations occur in pools of antigenically stimulated cells that have escaped the differentiating effects of infection during the first year or two of life, and that there may be an abnormal immune response in predisposed patients. There is indeed evidence of an association of ALL with a specific HLA antigen, but the large United Kingdom Childhood Cancer Study, which was designed in part to test the delayed infection hypothesis, has shown that early infections are not protective but in fact are associated with an excess of childhood leukaemia (Roman et al, 2009). In addition, the delayed infection hypothesis would have to explain the clusters associated with population mixing, which have not spared younger children.

7.17 While it may yet be impossible to determine the cause of an individual child’s leukaemia, there is much evidence to suggest that factors other than

radiation are likely to be important in many cases, and that these factors may include the existence of predisposing and spontaneously occurring genetic mutations, an abnormal immune response, and some role for what might apparently be relatively trivial common childhood infections.

Review of clinical and laboratory features of children with acute leukaemia living within 10 km of an NPP

7.18 COMARE undertook a characterisation of the cases of acute leukaemias in a set of young children (0–4 years of age) with residence at birth within 10 km of an NPP (including Calder Hall) born between 1962 and 1999 (and therefore diagnosed between 1962 and 2004). Each of these cases was compared with three matched controls (children under 5 years of age, diagnosed with leukaemia and resident at birth more than 50 km from any NPP), in order to establish any clinical and laboratory features specific to those cases close to an NPP. The subgroups that were included for analysis were those cancers classified in ICCC-3 as Group Ia (ALL), Ib (AML) and Ie (other leukaemias). These cases and controls were therefore similar to the cases in the analysis described in Chapter 6, the differences resulting from the use of cases from a different NRCT study. The principal difference is the use of the child's residence at birth, but it may be argued that this is at least as relevant an indicator of their proximity to an NPP as residence at the time of diagnosis: all the diagnoses were made before the age of 5 years and the cancer had presumably been latent for some time, if not actually since birth.

7.19 Of the 56 cases with diagnosis of acute leukaemia (Table 7.1), as would be expected, the great majority of both cases and controls had ALL (44 cases vs 145 controls, 78.6% vs 86.3%), with AML less common (9 cases vs 18 controls, 16.1% vs 10.7%), while other types of leukaemia (mature B-cell and unspecified and other specified) were much more rare.

7.20 The total white blood cell count at the time of diagnosis was available for all patients; there was no significant difference between the two groups (see Table 7.1).

7.21 Table 7.2 gives summary results of immunophenotypic data for ALL. In total, data are available for 35 cases and 110 controls. Of these, the paucity of T-cell and pre-B-cell subtypes of ALL in cases compared with controls (0% vs 12% and 0% vs 11%, respectively), and conversely the higher proportion of common ALL in cases compared with controls (91% vs 75%), is notable. The odds ratio for common ALL immunophenotype compared with the total of other immunophenotypes of ALL is statistically significant (OR = 3.64, 95% CI = 1.91–6.90, P = 0.01). Little scientific interest attaches to this observation, however, since the difference is driven by the deficit of the rare immunophenotypes near NPPs rather than an excess there.

7.22 Cytogenetic data are also available for some patients with ALL. These data may be affected by the time of diagnosis. The Philadelphia chromosome was described in 1960 (Nowell and Hungerford, 1960), and chromosome banding was not in use until after 1973. Other techniques, such as fluorescence *in situ* hybridisation (FISH), were also not in routine use until the 1990s. Where available (see Table 7.3), in comparison with cases, the control group has a higher incidence of cytogenetic abnormality (eg HeH). However, the number of cases with some of the specific abnormalities present is too small to warrant further statistical testing.

7.23 The majority of both cases and controls were enrolled in clinical trials (59% and 67%, respectively). Some additional data were available for these patients, which will need further analysis, but there do not appear to be major differences between cases and controls for haemoglobin or platelet count, or for organomegaly, mediastinal mass or Down's syndrome.

Table 7.1 Classifications of acute leukaemia cases and controls

Age at diagnosis (years)	Cases	Controls
Range	0–4	0–4
Mean	2.3	2.2
Median	2.5	2
Sex		
Males	31	93
Females	25	75
Diagnosis		
ALL, L1 or L2 *	44	145
ALL, L3 (mature B-cell)*	1	0
AML	9	18
Unspecified and other specified	2	5
White cell count		
Range	2–354	1–900
Mean	46	68
Median	17	14
Trial status		
Enrolled	33	112
Not enrolled	23	56

* L1, L2 and L3 refer to the French-American-British classification of ALL – see the glossary.

Table 7.2 Immunophenotypes for ALL cases and controls with available data

Immunophenotype	Cases	Controls
Mature B-cell	1	0
Common	32	82
Null-cell	2	3
Pre-B (cytoplasmic μ positive)	0	12
T-cell	0	13

Table 7.3 Cytogenetic data for cases and controls with ALL (it should be noted that not all patients were tested for these abnormalities)

Cytogenetics		Cases	Controls
t(12;21)	Absent	8	25
	Present	5	7
HeH	Absent	13	29
	Present	6	37
t(1;19)	Absent	19	62
	Present	0	3
t(9;22)	Absent	19	67
	Present	0	1
MLL	Absent	18	65
	Present	1	3
T-ALL	Absent	17	59
	Present	0	4

Cancer registration in the United Kingdom, France, Germany and Switzerland

7.24 Childhood cancer is rare and much less common than adult cancer. Of all childhood cancers, leukaemia occurs most frequently. In the UK, the risk of an individual child being diagnosed with leukaemia before the age of 15 years is approximately 1 in 1600 (Cancer Research UK, 2007). In 2003, the number of cases of childhood leukaemia (0–14 years) in the UK was 470, with over half of these in children under 5 years of age*. For the period 1966–2000, the average annual increase in the recorded incidence of childhood leukaemias in the UK was 0.68% per year (Stiller, 2007), which may be due in part to improvements in the accuracy of diagnosis. Monitoring of incidence trends and provision of data for epidemiological studies is dependent on registration of cancer cases.

7.25 The role of the cancer registries has been to collect population-based data on the incidence of and survival from all cancers over periods of time. The system of cancer registration and the data available can vary widely between countries, which can have an impact on the methodology selected for subsequent analyses. Individual countries may operate regional or national cancer registries. COMARE has reviewed the cancer registration systems for the UK, France, Germany and Switzerland.

United Kingdom

Children

7.26 The National Registry of Childhood Tumours (NRCT) is maintained by the Childhood Cancer Research Group, Department of Paediatrics, University of Oxford. It is population-based for children under 15 years of age in England, Wales, Scotland and the Isle of Man from 1962 onwards and in Northern Ireland from 1993 onwards. It includes malignant neoplasms of all sites and non-malignant intracranial and intraspinal tumours. Registration of myelodysplasia is believed to be complete from 1990 onwards. Langerhans cell histiocytosis (LCH) is registered but some children treated outside paediatric oncology centres are not included. Cases are ascertained from the all-ages regional cancer registries of England and national cancer registries of Wales, Scotland and Northern Ireland, from specialised paediatric tumour registries in four English regions, from paediatric oncology centres affiliated to the Children's Cancer and Leukaemia Group (CCLG), from national clinical trials for childhood acute leukaemia and from death certificates. Consent is not required for registration. The NRCT is a member of the UK Association of Cancer Registries and participates in the regular exchanges of data on eligible cases between member registries. In recent years, 93% of cases in the NRCT have been notified from the general cancer registry system and 93% have also been notified through the CCLG. The NRCT is the designated lead registry for childhood cancer within the National Cancer Intelligence Network.

7.27 Four specialist children's tumour registries cover former health regions of England from varying dates, as follows:

North West (Manchester)	1954
West Midlands (Birmingham)	1957
Northern (Newcastle)	1968
Yorkshire (Leeds)	1974

7.28 Cases are ascertained from hospitals within their respective regions, from the corresponding all-ages regional cancer registry, and from the NRCT. A population-based study of childhood cancer in the South West region covered the period 1976–1985 (Foreman, 1994); this has recently been reactivated as the Bristol Childhood Cancer Research Registry.

* http://www.leukaemia.org/about-leukaemia/incidence-of-childhood-leukaemia (accessed December 2010).

7.29 The overall level of completeness of NRCT registration is thought to have been around 95% for children diagnosed with cancer in the early 1980s and is probably closer to 100% for recent years*. Completeness of registration of leukaemia and non-Hodgkin lymphoma in the NRCT during 1974–1983 has been estimated at 99% (Draper et al, 1991). By 2000, there were over 47,000 cases registered with the NRCT. This number had increased to over 80,000 by 2007. The NRCT is believed to be the most important supranational, population-based, specialist children's cancer registry in the world, based on its longevity, size of population at risk, and depth and quality of information (Stiller, 2007).

All ages

7.30 Cancer registration throughout England is carried out by a network of regional registries and coverage has been national from 1962 onwards. The regional registries all contribute to national data compiled under the auspices of the National Cancer Intelligence Network. Population-based national cancer registries have covered Scotland from 1959, Wales from 1962 and Northern Ireland from 1993. All of these regional and national registries are members of the UK Association of Cancer Registries. The UK is widely acknowledged as having one of the most comprehensive cancer registration systems in the world†.

7.31 Details of ascertainment methods have varied between registries and over the years, but all the UK cancer registries ascertain cases from hospitals within their respective territories, and exchange information on 'extra-regional' cases diagnosed or treated in a region other than that of the patient's residence. All the registries also ascertain cases from death certificates. In addition to malignant neoplasms of all sites, the registries hold details of cases of non-malignant neoplasms of certain sites, including intracranial and intraspinal, breast, cervix and bladder neoplasms. In the past, there has been considerable variation between registries in the use they have made of death certificates and the extent to which non-malignant diagnoses have been included.

France

Children

7.32 The French National Registry of Childhood Haematological Malignancies, maintained at Université Paris-Sud/INSERM, Villejuif, is a population-based registry of leukaemia and lymphomas diagnosed in children under 15 years of age throughout France from 1990 onwards. Myelodysplasia has been included since the registry began, and LCH since 2000. Cases are ascertained from paediatric oncology/haematology centres and other hospitals throughout the country.

7.33 The National Registry of Childhood Solid Tumours, maintained in the paediatric oncology unit of the Children's Hospital at Nancy, is a population-based registry of malignant solid tumours and non-malignant intracranial and intraspinal tumours diagnosed in children under 15 years of age throughout France from 2000 onwards. Cases are ascertained from paediatric oncology centres and other hospitals throughout the country. During 2000–2003 the proportions of registered patients notified from paediatric oncology units varied by diagnostic group, from 100% for retinoblastoma and liver tumours, to 78% for CNS tumours, and 64% for carcinomas.

7.34 There are also five regional childhood cancer registries, each covering several *départements*, as follows:

Lorraine *(four départements)*	1983 onwards
Provence – Alpes – Côte d'Azur – Corse *(eight départements of mainland France, and Corsica)*	1984

* http://www.ccrg.ox.ac.uk/datasets/registrations.htm (accessed December 2010).
† http://82.110.76.19/registration/organisation.asp (accessed December 2010).

Rhône – Alpes *(eight départements)*	1987
Brittany *(four départements)*	1991
Auvergne *(four départements)*	1986
extended to Limousin *(three départements)*	1991

7.35 They all ascertain cases from hospitals within their regions together with extra-regional hospitals (mainly in nearby regions or in Paris) that would also be expected to care for children with cancer from their populations. Finally, a local registry operated in the Val-de-Marne *département* (which contains the country's largest paediatric oncology centre, at Villejuif) from 1990 until the establishment of the national registry for solid tumours in 2000. During the 1990s, the regional and local paediatric registries covered 32% of the national population. None of the registries described above has used death certificates as a source of cases.

7.36 The proportions of the national population with coverage of childhood leukaemia and lymphomas in all the paediatric and all-ages cancer registries combined increased from 2% in 1975 to 33% in 1988, finally achieving 100% in 1990.

All ages

7.37 At present, there is no national cancer registration system in France for all ages. The FRANCIM (French Association of Cancer Registries) network includes 12 population-based cancer registries, each covering one or more *départements*. The earliest of these commenced in 1975.

7.38 These registries cover a total of 14% of the national population for all types of cancer and 15% for leukaemia and lymphomas. As with the paediatric registries, cases are registered from hospitals but not from death certificates.

Germany

Children

7.39 The German Childhood Cancer Registry (GCCR) is maintained by the Institute for Medical Biostatistics, Epidemiology and Bioinformatics, University of Mainz. It covers the population of children under 15 years of age in the former West Germany (including West Berlin) from 1980 onwards and the whole of Germany (including the former East Germany) from 1991 onwards. Cases are ascertained directly from hospitals and from entries to clinical trials. Consent is required for registration but this is seldom refused. Death certificates are not used for case ascertainment. Non-malignant intracranial and intraspinal neoplasms, myelodysplasia and LCH are included. The ascertainment rate is believed to be about 95% for most diagnostic groups since 1987 (GCCR, 2009; Robert Koch Institute, 2010). It is somewhat less for CNS tumours, although ascertainment has improved considerably since 1990. Incidences for all malignancies in 1980–1982 were about 30% below the later 1980s levels and rose from about 1983 onwards. This does, however, differ considerably by diagnosis; for ALL and AML the ascertainment was almost complete from 1980 onwards. The GCCR was founded in 1980 in close cooperation with the clinical trials. Diagnoses where clinical trials were already established in 1980 (eg ALL and AML) had almost complete ascertainment from 1980 onwards[*]. From 1980–2000, 29,980 cases were registered with the GCCR. Childhood cancer was included in the all-ages national cancer registry of East Germany up to 1989.

All ages

7.40 The national cancer registry of East Germany operated from 1953 to 1989. The data have since been frozen, but anonymised records have been made available to international projects including 'Cancer Incidence in Five Continents', 'International Incidence of Childhood Cancer', 'Automated Childhood Cancer Information System' and 'Eurocare'. Since 1991 the whole of the former East

* Personal communication from Dr Spix.

Germany has been covered by the Common Cancer Registry (CCR). Cases are ascertained from regional cancer centres and other hospitals and also from death certificates. Cancer notification became mandatory in the six states covered by the CCR at different dates between 1993 and 2006, and, by 2004, the CCR covered 21% of the total population of Germany.

7.41 In the former West Germany, each cancer registry covers the whole or part of a federal state. The Hamburg Cancer Registry, founded in 1926, is one of the oldest in the world, although with gaps in coverage during the Second World War and during the early 1980s; it covers 2.1% of the national population. The Saarland Cancer Registry started in 1967 and covers 1.3% of the national population. The Münster Cancer Registry began in 1985 and covers 3.1% of the national population. Population-based data for the remainder of Germany are only available from 1994 or later, depending on the region.

Switzerland

Children

7.42 The Swiss Childhood Cancer Registry is a population-based registry of malignant neoplasms, non-malignant intracranial and intraspinal tumours, and LCH diagnosed in children under 16 years of age in the whole of Switzerland. Cases are ascertained from the nine paediatric oncology centres and other hospitals, all-ages cancer registries in the cantons where these exist (see below), and death certificates. Consent was required for registration up to 2007, but since June of that year the registry has been permitted to collect data without consent. The registry includes children diagnosed from 1976 onwards. An evaluation of completeness found that in 1985–1988 the registry included 91% of all childhood leukaemia cases in the all-ages cantonal registries then in existence, and 80% of all children in the country who died of leukaemia in 1989. The total annual numbers of registrations increased sharply between 1986–1990 and 1991–1995, suggesting that ascertainment is much more complete for the 1990s onwards.

All ages

7.43 General cancer registration is organised at cantonal level, although a few registries cover more than one canton. There are now ten registries covering 14 cantons, corresponding to 62% of the national population. Coverage is much higher in the Latin (French and Italian speaking) part of the country, 98%, than in the German speaking part, 47%. The oldest registries, established in Basel and Geneva in 1970, cover 12% of the national population. As more registries were started, coverage increased to 14% in 1972, 22% in 1974, 46% in 1980 and 53% in 1989.

Summary

7.44 Childhood leukaemia is not a single, homogeneous disease and both ALL and AML have definable subtypes. It may not yet be possible to establish the cause of an individual child's leukaemia; however, evidence suggests that factors other than radiation (including the existence of predisposing and spontaneously occurring genetic mutations and an abnormal immune response) are likely to be important in many cases.

7.45 Except for the relative paucity of T-cell and pre-B-cell ALL, and conversely the higher proportion of common ALL (cALL), among children with ALL resident within 10 km of an NPP at the time of diagnosis, the cases living near an NPP appear not to differ from a larger group of control patients. The implications of the immunophenotypic disparity, for those cases where the data are available, between cases and controls with ALL are unclear. In a group of 35 children with ALL, it would be expected to see around five children with T-cell disease, although this immunophenotype is more common in older children than the group of cases and controls analysed here. It will be important to see if this finding is replicated in other studies of the clinical and laboratory features of children living in proximity to an NPP at the time they develop ALL. In addition, it may be possible to characterise further biological features of cases

and controls, although such tests will be limited by the availability of suitable biological material such as DNA.

7.46 Childhood cancer is rare, being much less common than adult cancers. There is a requirement for a specialised, comprehensive childhood cancer registration system that maintains a high level of ascertainment for epidemiological analyses investigating incidence and mortality rates of childhood cancers. Cancer registration systems vary between countries and may be operated on a regional or national basis. From the four countries considered, it is apparent that there are differences in the sources of cases and whether death certificates are used. The UK is recognised as having one of the most comprehensive systems for cancer registration and the NRCT in the UK is one of the largest and longest running cancer registries in the world. The major strengths of the NRCT lie in the comprehensive ascertainment of cases, the population base, and the collection and validation of a wide range of data items, including histological diagnosis, initial treatment, follow-up and other clinical information.

CHAPTER 8

OTHER FACTORS – NUCLEAR POWER PLANTS, DISCHARGES AND DOSES TO THE PUBLIC

8.1 It is important to recognise that there may be differences in other factors that may cause variation in observed results when considering and comparing the incidence of childhood leukaemia in the vicinity of NPPs in several countries. This chapter considers the types of nuclear reactors in use; their geographical locations, the discharges of radionuclides from the plants and the associated radiation doses to the general population for selected countries. The European countries of the United Kingdom*, France, Germany and Switzerland were selected for comparison, based on the availability of data and past/future studies on the incidence of childhood cancer in the vicinity of NPPs.

Reactor types in the United Kingdom, France, Germany and Switzerland

8.2 In the United Kingdom, France, Germany and Switzerland the nuclear reactors currently employed in electricity generation all use moderators to slow neutrons to thermal energies, use uranium (as metal or oxide) as fuel (some are capable of using mixed uranium and plutonium oxide fuel), and can be classified by their coolant and moderator systems. They all release airborne radioactive material and liquid radioactive effluents, and may also generate enhanced levels of direct radiation to the public living close to the reactor site. The majority of NPPs in France, Germany and Switzerland are built beside rivers, whereas British operating NPPs are all built on the coast. The radionuclides most frequently released include those of the noble gases argon-41, krypton-85 and xenon-133, and tritium (hydrogen-3), carbon-14, cobalt-60, iodine-131 and caesium-137. These releases typically result in annual effective doses to the public in the range 0.01–0.1 mSv; such doses are small compared to doses arising from ubiquitous natural background radiation. Detailed descriptions of reactor types are given in Appendix B. A summary of reactor types and locations for the UK, France, Germany and Switzerland is given in Table 8.1.

Table 8.1 Types of nuclear reactors in operation in the United Kingdom, France, Germany and Switzerland in 2007 (ASN, 2007; BMU, 2008; HSE, 2007; HSK, 2007)

Country	Number of reactors	Number of sites	Type of reactor *			
			PWR	BWR	AGR	Magnox
United Kingdom	19	9	1	0	14	4
France	58	19	58	0	0	0
Germany	17	12	11	6	0	0
Switzerland	5	4	3	2	0	0

* PWR pressurised water reactor, BWR boiling water reactor and AGR advanced gas cooled reactor.

* It should be noted that although the reports cited here refer to the United Kingdom, there are no nuclear reactors in Northern Ireland.

United Kingdom

8.3 The UK report produced in relation to the Convention on Nuclear Safety, dated September 2007 (HSE, 2007), states that the UK has 19 power reactors in operation at nine different sites, these being 14 AGRs, four Magnox reactors and one PWR, as listed in Appendix C.

8.4 The twin reactors sites at Oldbury and Wylfa contain the four currently operating Magnox reactors (gas cooled reactors). All four of these reactors employ pre-stressed concrete pressure vessels. All the Magnox reactors with steel pressure vessels were safely shut down by the end of 2006; their status as stated in September 2007 was as follows:

Berkeley	2 reactors	Decommissioning
Bradwell	2 reactors	Decommissioning
Calder Hall	4 reactors	Shut down
Chapelcross	4 reactors	Shut down
Dungeness A	2 reactors	Shut down
Hinkley Point A	2 reactors	Decommissioning
Hunterston A	2 reactors	Decommissioning
Sizewell A	2 reactors	Shut down
Trawsfynydd	2 reactors	Decommissioning

8.5 In addition, there are research reactors, some of which provided electricity to the national grid. The larger ones are located at Dounreay, Harwell, Windscale (Sellafield) and Winfrith, all of which are in the process of being decommissioned.

France

8.6 The French report produced in relation to the Convention on Nuclear Safety, dated July 2007 (ASN, 2007), states that France had 58 power reactors, all of which are PWRs. They were connected to the grid between 1977 and 1999 (see Appendix C). They supplied approximately 80% of the electricity generated in France. The power reactors are located at 19 sites and there are two to six reactors per site. There were thirty-four 900 MWe reactors (CP0 and CP1 series), twenty 1300 MWe (P4 series), and four 1450 MWe reactors (N4 series). A European pressurised water reactor (EPR) is under construction at Flamanville.

8.7 In addition to the NPPs, France has 11 research reactors of various types with thermal powers ranging from 0.1 kilowatt thermal (kWth) to 350 kWth.

Germany

8.8 The German report produced in relation to the Convention on Nuclear Safety, dated April 2008 (BMU, 2008), states that Germany had 17 power reactors in operation at 12 different sites; 11 PWRs and six BWRs (see Appendix C). In addition, there was one PWR that had been shut down in 2005 where decommissioning had been proposed, but the authorising body had not given approval to the decommissioning programme. There were also 19 permanently shut down NPPs and six reactor projects that were abandoned.

8.9 Germany has four research reactors with a capacity over 50 kWth and eight small training reactors; ten research reactors have been decommissioned and were being dismantled, and another 24 research reactors had already been fully dismantled.

Switzerland

8.10 The Swiss report produced in relation to the Convention on Nuclear Safety, dated July 2007 (HSK, 2007), states that Switzerland had five power reactors located at four different sites as follows: Breznau I 365 MWe PWR, Breznau II 365 MWe PWR, Muhleberg 355 MWe BWR, Gösgen 970 MWe PWR and Leibstat 1185 MWe BWR. The fuel for the BWRs is uranium oxide; the PWRs use the same fuel, but may also use mixed oxide fuel.

Radionuclide discharges from nuclear reactors

8.11 Radionuclide discharges may be defined as legitimate planned and controlled releases into the environment, within limits authorised by the regulatory body, of liquid or gaseous radioactive materials that originate from regulated nuclear facilities during normal operation (NEA, 2003). The design and operation of NPPs can largely determine whether radionuclides are discharged as gaseous or liquid effluents. For example, for tritium, liquid discharge is the preferred route because it results in a smaller dose to the public than gaseous discharge (at Sizewell B, for example, gaseous discharges of tritium are less than 5% of liquid discharges). The quantities of radioactive effluents that are discharged from NPPs depend on fuel quality and integrity, reactor coolant chemistry control, used fuel storage ponds chemistry control, outage practices, and abatement plant efficiency. Typical releases of radioactive materials from the different reactor designs are shown in Table 8.2.

Table 8.2 Typical releases of radioactive materials from nuclear reactors (NEA, 2003)

	Typical release from types of reactor * (TBq per GWa †)		
Radioactive material	**BWR**	**PWR**	**GCR**
Noble gases	100	10	1000
Tritium gas	1	2	2
Carbon-14	0.6	0.1	1
Iodine-131	0.001	0.001	0.001
Particulates	0.5	0.0001	0.0001
Tritium liquid	0.9	10	100
Other liquid	0.01	0.01	0.6

* PWR pressurised water reactor, BWR boiling water reactor and GCR gas cooled reactor.
† TBq per GWa = terabecquerel per gigawatt annual.

8.12 Nuclear power plants and the management of radioactive waste and spent nuclear fuel are subject to international agreements and declarations that may impose obligations on a country's national policies and procedures. These include the following conventions, for example.

(i) *Convention on Nuclear Safety* is an international convention, which aims to improve nuclear safety worldwide (IAEA, 1994). The Convention applies to land-based civil NPPs.

(ii) *Joint Convention on the Safety of Spent Nuclear Fuel Management and on the Safety of Radioactive Waste Management* aims to achieve and maintain a high level of safety worldwide in spent fuel and radioactive waste management (IAEA, 1997). The Joint Convention applies to spent fuel and radioactive waste arising from civil NPPs and to radioactive waste arising from other nuclear activities, such as nuclear fuel fabrication and reprocessing of spent nuclear fuel. It also applies to radioactive waste arising from non-nuclear operations, such as the production of isotopes for medical applications.

(iii) *OSPAR Convention for the Protection of the Marine Environment of the North-East Atlantic* guides international cooperation on protecting the marine environment of the North-East Atlantic (OSPAR, 2003). The OSPAR Radioactive Substances Strategy imposes requirements on all countries discharging radioactive effluents into the North-East Atlantic. The Strategy seeks progressive and substantial reductions of discharges, emissions and losses of radioactive substances. It applies only to discharges to the marine environment.

8.13 Member states of the European Union are legally bound by the provisions of the Euratom Treaty (EC, 1957). The Treaty aims to guarantee high safety standards for the public and prevent nuclear materials intended principally for civilian use from being diverted to military use. It also includes obligations regarding management of radioactive discharges – for example, Article 37 deals with the potential transboundary effects of radioactive discharges. Of the countries selected for study in this chapter only the UK, France and Germany are EU member states.

8.14 Under Article 33 of the Euratom Treaty, EU member states have to implement appropriate provisions to ensure compliance with the basic safety standards established under Article 31. The Basic Safety Standards (BSS) Directive (EC, 1996) lays down standards for the protection of the health of workers and the general public against the dangers arising from ionising radiation. The BSS Directive requires, among other things, that all exposures to ionising radiation of any member of the public and of the population as a whole resulting from the disposal of radioactive waste are kept as low as reasonably achievable (ALARA), economic and social factors being taken into account.

8.15 In 2004 the European Commission issued Commission Recommendation 2004/2/Euratom (EC, 2004), regarding standardised information on radioactive airborne and liquid discharges into the environment from nuclear power reactors and reprocessing plants in normal operation. The recommendation considers each category of radioactive discharges and each type of nuclear installation. The following are listed as key radionuclides for NPP discharges, representing categories of radionuclides or a specific type of radiation, which are significant in terms of radiological impact and are suitable sensitivity indicators for measurement:

Airborne	Tritium, Carbon-14, Sulphur-35, Cobalt-60, Krypton-85, Strontium-90, Iodine-131, Xenon-133, Caesium-137, Plutonium-239/240, Americium-241
Liquid	Tritium, Sulphur-35, Cobalt-60, Strontium-90, Caesium-137, Plutonium-239/240, Americium-241

8.16 In the UK, discharges of radioactive waste to the environment are strictly controlled through the environmental permits or authorisations granted to NPP operators. In England and Wales, environmental permits are granted by the Environment Agency under the Environmental Permitting (England and Wales) Regulations 2010 (EPR 2010) (GB Parliament, 2010) and, in Scotland, the Scottish Environment Protection Agency (SEPA) grants authorisations under the Radioactive Substances Act 1993 (RSA 1993) (GB Parliament, 1993). For simplicity, the Environment Agency and SEPA will be referred to as the 'environment agencies'.

8.17 The environment agencies regulate all discharges of radioactive waste to the environment from an NPP. These include discharges into the atmosphere, surface waters and groundwater, disposals to land, and disposals by transfer to another site. The environment agencies require NPP operators to apply best available techniques (BAT) in England and Wales or best practicable means in Scotland (BPM) to managing and monitoring radioactive discharges (EA and SEPA, 2010).

8.18 The environment agencies place limits on radioactive discharges to the environment in environmental permits and authorisations for NPPs. The limit-setting process takes account of, for example, the radiation dose to members of the public, the magnitude of the discharges and plant performance indicators. Discharge limits are set to ensure that radiation doses to members of the public

remain well within the internationally agreed limits which are set out in the BSS Directive. The BSS requirements are implemented in England and Wales through the EPR 2010 and are implemented in Scotland through the Radioactive Substances (Basic Safety Standards) (Scotland) Direction 2000 (SEPA, 2000).

8.19 The requirements for reporting discharges are specified in the permit or authorisation for each nuclear site. The environment agencies have produced guidance to standardise reporting of radioactive discharges from nuclear sites in the UK (EA and SEPA, 2010).

8.20 The UK Government and devolved administrations have agreed that the same information on radioactive discharges as that required by the environment agencies from nuclear site operators should also be provided to the European Commission. The information reported by nuclear site operators may not necessarily include all the radionuclides listed in the relevant annex of Commission Recommendation 2004/2/Euratom (EC, 2004).

8.21 Since 2004, all nuclear sites and non-nuclear facilities in England and Wales have been required to report their discharges annually to the Environment Agency Pollution Inventory. In Scotland, since 2004, all nuclear sites have been required to report their discharges annually to the SEPA Pollution Inventory with the requirement extended to all non-nuclear sites in 2005. The list of radio-nuclides that may be reported to the EA/SEPA pollution inventories for gaseous and liquid discharges is given in Table 8.3. Discharges over the reporting threshold must be reported.

Table 8.3 Reported radionuclides in the EA/SEPA pollution inventories

Releases to air		**Releases to controlled waters**	
Annual reporting threshold	**Radionuclide**	**Annual reporting threshold**	**Radionuclide**
100 GBq	Tritium	1 MBq	Total alpha
1 GBq	Carbon-14	1 MBq	Total beta/gamma (not tritium)
100 GBq	Fluorine-18	1 TBq	Tritium
100 MBq	Sulphur-35	100 MBq	Carbon-14
1 TBq	Argon-41	10 GBq	Sulphur-35
1 TBq	Krypton-85	10 MBq	Cobalt-60
1 TBq	Technetium-99m	100 MBq	Strontium-90
1 GBq	Ruthenium-106	1 GBq	Yttrium-90
10 MBq	Iodine-125	1 GBq	Zirconium-95
1 MBq	Iodine-129	100 MBq	Niobium-95
10 MBq	Iodine-131	1 GBq	Technetium-99
1 TBq	Xenon-133	1 GBq	Ruthenium-106
100 MBq	Caesium-137	10 GBq	Antimony-125
1 GBq	Radon-222	100 MBq	Iodine-129
10 MBq	Uranium alpha	10 MBq	Caesium-134
1 MBq	Plutonium alpha	100 MBq	Caesium-137
1 MBq	Americium-241	1 GBq	Cerium-144
		10 MBq	Thorium-230
		10 MBq	Thorium-232
		100 MBq	Uranium alpha
		100 MBq	Neptunium-237
		100 MBq	Plutonium alpha
		10 GBq	Plutonium-241
		100 MBq	Americium-241
		10 GBq	Curium-242

8.22 Figure 8.1 shows the ranges of annual discharge quantities from NPPs in the UK, France, Germany and Switzerland for selected radionuclides for 1999, on a logarithmic scale with each marker representing an individual NPP. This year was selected as being within the period studied in the epidemiological analyses of this report, allowing for a latency period of leukaemia, and with reasonably comprehensive data available for the selected radionuclides. It also corresponded to available data on implied effective doses (see paragraphs 8.31 and 8.36). Data were collected from the relevant regulatory authorities for each of the four countries for each NPP as far as possible. To ensure that 1999 was not atypical for the quantities of discharges recorded, data were also collected for 2000 and 2001 to highlight any trends or ambiguities in the values. Full details of the selected gaseous and liquid discharges (1999–2001) from each of the NPPs, where available, for the UK, France, Germany and Switzerland are given in Appendix D.

8.23 Inconsistency in radionuclide reporting between the selected countries is evident. For example, gaseous carbon-14 discharges were not available for France for 1999 and liquid carbon-14 discharges were not available from any of the countries. This inconsistency did not improve between 1999 and 2001, based on the data obtained from the regulatory authorities. European Commission Recommendation 2004/2/Euratom required reporting of gaseous carbon-14 discharges from all nuclear installations, but liquid carbon-14 discharges from nuclear reprocessing plants only, not from nuclear power plants (EC, 2004).

8.24 Separate analysis of discharges from NPPs for 1990–1994 highlighted substantial differences in the quantities of radionuclides released from individual reactors (NEA, 2003), which mirror the ranges shown in Figure 8.1. It was thought that the wide distribution could be due to the type of reactor, the integrity of the fuel, the waste handling systems, the load levels, and procedures and maintenance operations conducted, as well as variations in reporting and differences in measuring practices (NEA, 2003).

8.25 Certainly for 1999, the ranges of the selected radionuclide discharge quantities in the UK were the largest of all four countries considered in this chapter. It might therefore be expected that, if there is an increased incidence of childhood leukaemia associated with radiation exposure from radionuclide discharges (particularly tritium) from NPPs, there would be evidence of this in the UK, even taking into account the coastal locations of the NPPs. Both previous and current analyses suggest this is not the case.

8.26 However, it is not sufficient solely to consider the quantities of radionuclides released into the environment to determine the impact on the general population. An estimate of the dose received is required, which can be calculated using the discharge data together with information regarding the siting of an NPP and the local environment. The general public is exposed to radiation from a variety of sources and doses from radioactive discharges from NPPs contribute to that proportion of the annual effective dose that is due to man-made non-medical exposure (which also includes, *inter alia*, occupational exposure and nuclear weapons testing fallout). Article 13 of the BSS Directive requires that the annual effective dose to the most exposed members of the public (excluding natural background and medical procedures) must not exceed 1 mSv (EC, 1996).

8.27 Radioactive material is released from both nuclear installations (power plants, reprocessing plants, and defence and research establishments) and non-nuclear sites (hospitals, universities, industries and research centres). In 2005, the average annual effective dose from radioactive waste discharges was estimated to be 0.9 μSv for the UK (Watson et al, 2005). The average annual

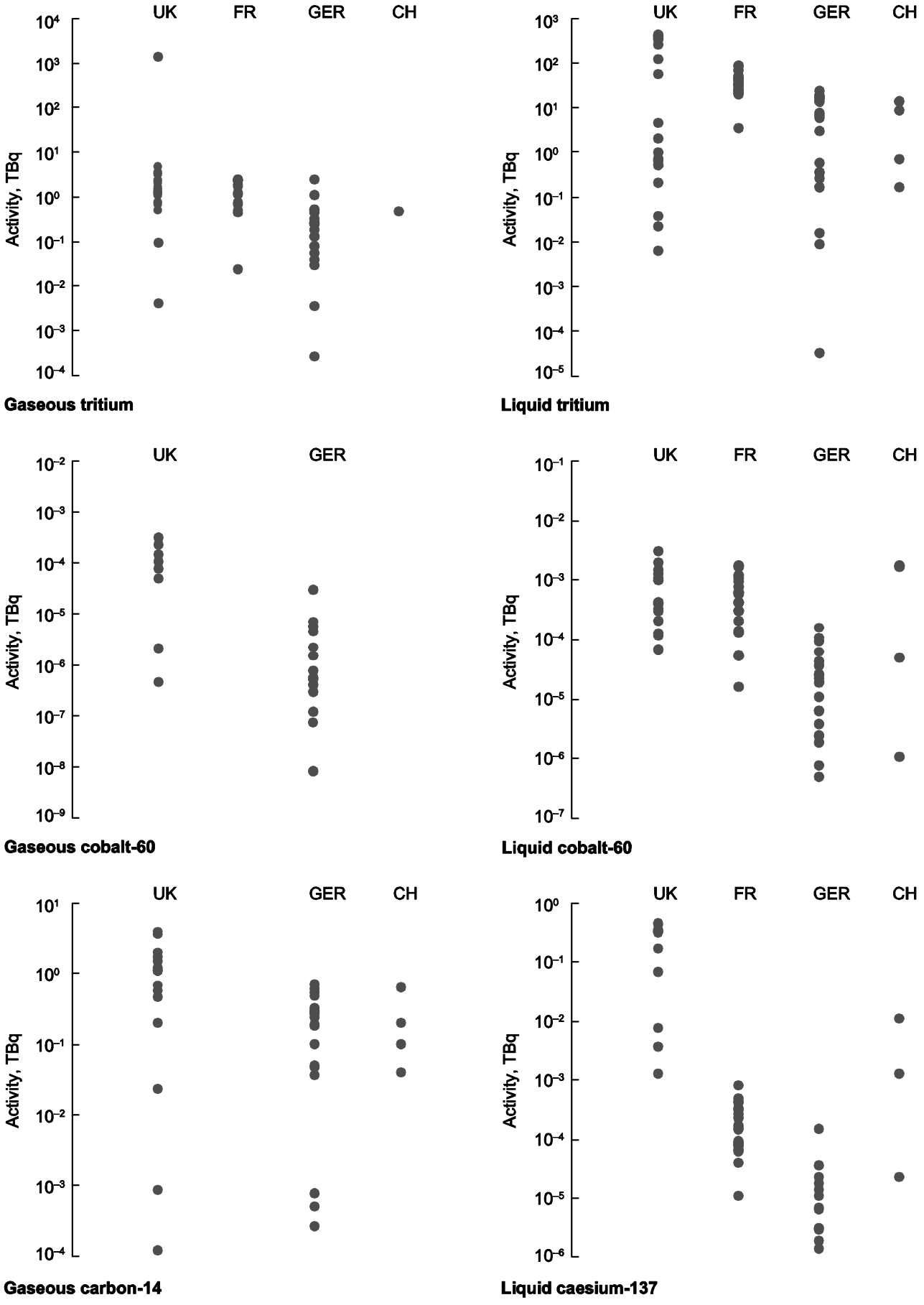

Figure 8.1 Reported annual discharges (gaseous and liquid) of specific radionuclides from NPPs in selected countries in 1999 (UK, United Kingdom; FR, France; GER, Germany; CH, Switzerland). Each marker represents an individual NPP and is plotted on a logarithmic scale

Table 8.4 Radiation doses from natural (background) and medical exposures for selected European countries compared with the dose estimated from radioactive waste discharges

Country	Exposure source	Average annual effective dose (mSv)	Source
United Kingdom	Natural	2.2	Watson et al, 2005
	Medical exposures	0.4	
	Radioactive waste discharges	0.0009	
France	Natural	2–2.5	Billon et al, 2005
	Medical exposures	0.66–0.83	SCANFF et al, 2008
	Radioactive waste discharges	<0.01	ASN, 2009
Germany	Natural	2.1	SSK, 2008
	Medical exposures	1.9	
	Radioactive waste discharges	<0.01	
Switzerland	Natural	4.3	OFSP, 2009
	Medical exposures	1.2	
	Radioactive waste discharges	<0.05	

effective dose from natural and medical sources of exposure in the UK was estimated to be 2.6 mSv (see Table 8.4). Liquid discharges accounted for an estimated average annual effective dose of around 0.7 μSv (10% of which is from the nuclear industry); gaseous discharges resulted in an estimated average annual effective dose of around 0.2 μSv (50% of which is from nuclear sites) (Watson et al, 2005). Therefore the estimated average annual effective dose resulting from discharges from the nuclear industry in the UK is around 0.0065% of the average annual effective dose from natural and medical sources of exposure.

8.28 Radiation exposure of the local and wider populations from the release of radioactivity into the environment can follow various exposure pathways (ingestion, inhalation and external exposure), the contributions of which are dependent on the method and type of the discharge.

8.29 The radioactivity monitoring programmes in the UK have several purposes (EA et al, 2010). Long-term trends in the concentrations of radioactivity over time and distance from nuclear licensed sites can be followed with the help of ongoing monitoring. Radionuclide dispersion around each site is assessed through monitoring the environment. Radiation doses to the public are assessed using both food and environmental results, for comparison with the UK statutory dose limits. This type of retrospective dose assessment considers the people who would be most exposed to the radiation.

8.30 It is also possible to assess the implied doses based on the reported discharges (both gaseous and liquid) of radioactive material from NPPs through the use of specific modelling software (EC, 2008). Assessment of dose is complex and not solely dependent on the distance from a nuclear installation. Consideration is made of the various exposure pathways, habit data for the local population, meteorological data, and population and agricultural production distributions. The reported total quantities of radioactivity discharged annually allow an average annual effective dose to be assessed on the assumption that the releases are at a constant rate throughout the year. However, in practice, radioactive material is not discharged continuously and this will result in some fluctuations in the associated dose with time.

8.31 The European Commission has published the results of a study assessing the implied effective doses to the population of the European Union based on reported discharges of radioactive material from NPPs in EU member states and reprocessing sites for the period 1997 to 2004 (EC, 2008). Doses from gaseous and liquid discharges are calculated separately and, as the assessments rely solely upon the statutory reporting requirements of each member state, the values should be regarded as an indication of the doses received.

8.32 Figure 8.2 shows, on a logarithmic scale, the wide range of implied effective doses to an adult member of the representative critical group from reported gaseous discharges at two distances from selected NPPs in the EU in 1999, each marker representing an individual NPP. The members of the representative critical group are people who eat higher than average amounts of the food that is produced where they live. For most people in the population the doses will be substantially lower as their food will be a mixture from many sources.

8.33 It is apparent from Figure 8.2 that, in 1999, the UK had the greatest spread and highest values of implied annual effective doses from gaseous discharges of the three countries shown. The highest implied annual effective dose at 500 m from an NPP of 0.14 mSv was well below the 1 mSv per year dose limit for the general public. Although the implied annual effective doses from gaseous discharges decrease with increasing distance from the NPP, the decrease will not have exact radial symmetry due to meteorological and geographical factors. Furthermore, the impact from liquid discharges also needs to be included to provide a total dose estimate.

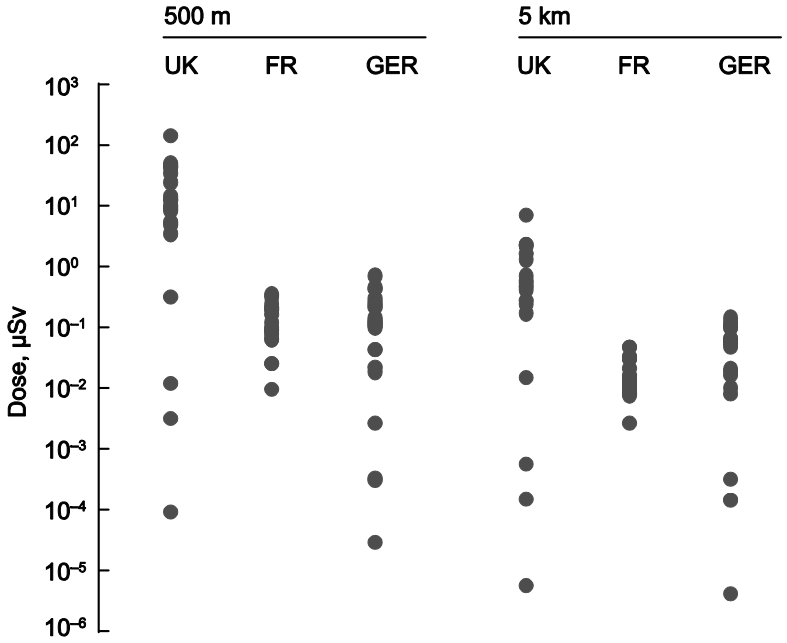

Figure 8.2 Implied annual effective doses to an adult member of the representative critical group* from reported annual gaseous discharges at two distances from selected NPPs in the EU in 1999 (UK, United Kingdom; FR, France; GER, Germany). Each marker represents an individual NPP and is plotted on a logarithmic scale (EC, 2008)

* ICRP Publication 101 'Assessing Dose of the Representative Person for the Purpose of Radiation Protection of the Public and the Optimisation of Radiological Protection' uses a new term in relation to the general public, namely 'representative individual' – this is broadly the same as the 'representative critical group'.

8.34 The doses associated with liquid discharges are more complicated to assess and depend significantly on the type and destination of the discharge (ie into rivers, estuaries or the sea, see Figure 8.3). The distribution of doses in the population associated with liquid discharges is not strongly related to distance from the site. A number of NPPs in the EU discharge into the same river system, which has to be taken into consideration in the assessments. The doses associated with each section of a river where a discharge occurs were calculated on the basis of the reported annual discharges, including contributions from discharges further upstream. The calculations used models for the dimensions, sedimentation rates and flow rates of the river. Exposure pathways considered for critical groups living close to the rivers included ingestion of radionuclides from drinking water and fish and external exposure to radionuclides in riverbank sediments. Doses to the critical group living in coastal regions may also include any contributions from discharges into a river which flows into the sea in that vicinity, in addition to the direct marine discharges from coastal sites. Exposure pathways considered for coastal-living critical groups included ingestion of sea fish, molluscs and crustaceans; external exposure to radionuclides in beach sediments; external exposure to contaminated fishing gear; and inhalation of sea spray. The coastal location of British NPPs results in liquid marine discharges rather than into river systems. The exception is Trawsfynydd in Wales, which discharges into a lake (classed as river), and where the ingestion of fish rather than drinking water was used for the calculations, since the water from the lake is not consumed by people.

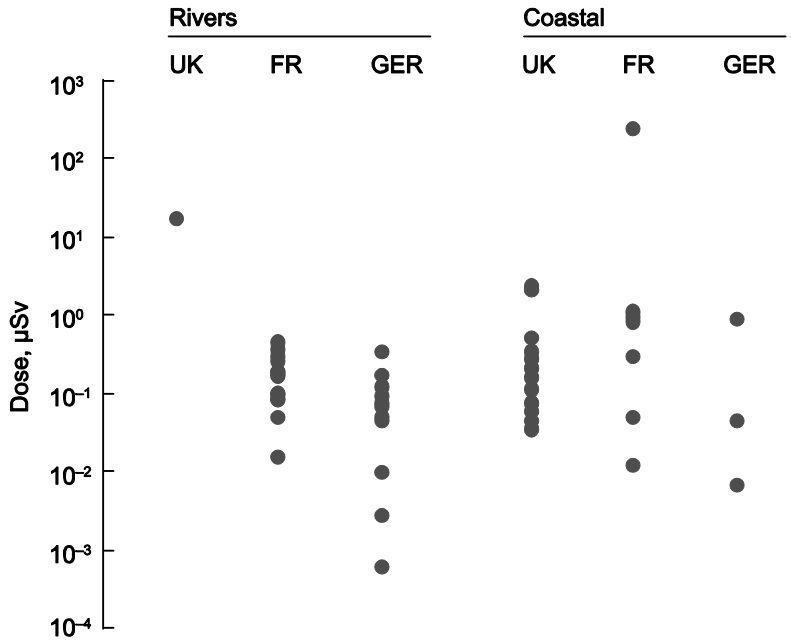

Figure 8.3 Implied annual effective doses to an adult member of the representative critical group living near rivers or the coast, from reported annual liquid discharges from selected NPPs in the EU in 1999 (UK, United Kingdom; FR, France; GER, Germany). Each marker represents an individual NPP and is plotted on a logarithmic scale (EC, 2008)

Doses to adults living near rivers include upstream contributions and are based on reported discharges to rivers; doses to adults living near the coast include contributions from inland and coastal sites and are based on reported discharges

8.35 These calculations for implied doses use models of the lifestyle and activity of members of the public living in the vicinity of an NPP and are intended to represent an upper limit to the exposure an individual might experience. For cancer incidence in a particular locality, it is more relevant to consider the average exposures in the population, which are likely to be substantially lower than those for the representative critical group.

8.36 As noted previously, calculations of these implied doses to the representative critical group are greatly dependent on the reported discharges from the nuclear sites, which do not necessarily constitute the complete discharge inventory. Reporting practices for the radionuclides have varied in the past between countries and between types of nuclear installations within countries. For example, reporting of carbon-14 discharges has not been consistent within the EU – whilst the reporting of gaseous carbon-14 discharges from NPPs has been more reliable since 2002, for liquid carbon-14 discharges reporting has only been required for nuclear reprocessing plants but not for NPPs (EC, 2008). In the UK, there has been regular reporting of gaseous carbon-14 discharges and, since 2004, both gaseous and liquid discharges of carbon-14 above the threshold level have been required to be reported to the EA/SEPA pollution inventories from all nuclear installations.

8.37 The examples of discharges and implied doses presented in this chapter are for 1999 and may not be representative of the subsequent discharge quantities and associated doses, through to the present day. Data were collected on discharges for 1999–2001 to ensure that 1999 is not atypical for the countries and radionuclides selected. The OSPAR database shows that over the period 1990–2007, liquid discharges of tritium from NPPs in Europe remained relatively constant, although the discharges in 2007 (2936 TBq) were again lower than in 2006 (3304 TBq) and significantly lower than in 2005 (4160 TBq) (OSPAR, 2009). The most recent *Radioactivity in Food and the Environment* report (RIFE-15) for 2009 states that the discharges from the nuclear sector in the UK continue to be lower than in the past (EA et al, 2010).

8.38 Comprehensive radiological risk assessments were conducted by the then National Radiological Protection Board (NRPB, now part of the Health Protection Agency) on behalf of COMARE for its first four reports, addressing in turn the radiation-induced risk of childhood cancer (in particular, childhood leukaemia) in the vicinity of Sellafield, Dounreay, Aldermaston/Burghfield/ Harwell, and Sellafield again (Dionian et al, 1986, 1987; Simmonds et al, 1995; Stather et al, 1986). In general, radioactive discharges from these nuclear facilities have been greater than those from NPPs, especially at Sellafield and Dounreay, consequently leading to higher doses. However, these assessments demonstrated that the doses received from discharges from these sites have generally been smaller than those received from natural background radiation, and much smaller than the doses required to explain the excess cases of childhood leukaemia that have been reported from their vicinities. Doses received around Sellafield as a consequence of operations at the site have been greatest in the UK and are at least a factor of 100 too small to account for the excess cases observed in the nearby village of Seascale.

8.39 Suggested reasons why these radiological risk assessments may have seriously underestimated the risk of radiation-induced childhood leukaemia resulting from discharges (Crouch, 1986) have been investigated, with the conclusion that even after accounting for the inevitable uncertainties present in the assessments, the doses received from radionuclides discharged from these nuclear installations remain far too small to be the cause of the excess incidence of childhood leukaemia in their vicinities (COMARE, 1989; Stather et al, 1988; Wheldon, 1989).

8.40 Conversely, it has been proposed by Fairlie (2008, 2009a–c, 2010a–c) and others (eg Nussbaum, 2009) that radioactive material discharged from German NPPs is responsible for the elevated risk of leukaemia among young children living in the vicinity of these sites, as reported in the KiKK study. As noted by the SSK (2008), this would imply that the risk of childhood leukaemia resulting from discharges has been underestimated by considerably more than a factor of 1000. Fairlie points to the possible relevance of discharges of tritium and carbon-14, and to the exposure of the embryo and foetus *in utero* to these radionuclides (Fairlie, 2009a,c, 2010a–c).

8.41 The impact on the risk of childhood leukaemia of tritium releases into the environment has been considered previously. A hypothesis was put forward that the childhood leukaemia cluster in the vicinity of the Krümmel NPP in northern Germany was associated with tritium discharges from the plant. Comparison of childhood leukaemia incidence in the vicinity of the Krümmel NPP in Germany and of the Savannah River Site (SRS), USA, found no evidence of an increased rate of incidence around the SRS, despite tritium discharges from the SRS being several orders of magnitude higher than those from the Krümmel site (Grosche et al, 1999). Although several limitations with the study were recognised, the results suggested that tritium discharges were not responsible for the increase in cases of childhood leukaemia around the Krümmel NPP. It is also of note that the Northern Germany Leukaemia and Lymphoma (NLL) study, a case–control study that covered an area including Krümmel and reconstructed individual doses from discharges from NPPs, could not explain the excess of cases of childhood leukaemia in the vicinity of Krümmel in terms of the dose received from routine discharges (Hoffmann et al, 2003, 2008).

8.42 The Committee Examining Radiation Risks of Internal Emitters (CERRIE) examined the issue of radioactive material inadvertently taken into the body ('internal emitters') (CERRIE, 2004). Of particular concern were those radionuclides emitting short-range radiations, such as alpha particles, that essentially pose no risk to health if present outside the body. The ninth COMARE report reviewed the findings of the CERRIE report and concluded that although uncertainties in risk estimates are generally greater for internal emitters than for irradiation from external sources, risks arising from radioactive material taken into the body have not been radically underestimated (COMARE, 2004). COMARE recommended continued research into the biokinetics of, and tissue responses to, internal emitters in its ninth report.

8.43 As a result of the CERRIE report and a separate recommendation in the ninth COMARE report, a subgroup of the Advisory Group on Ionising Radiation was established to review the risks to health of exposure to tritium (AGIR, 2007). Although the AGIR report recommended that the relative biological effectiveness (RBE) of tritium be increased from one to two, it did not find that the risk of exposure to tritium had been underestimated to the large degree required to explain the KiKK study results, a finding with which Fairlie apparently concurs (Fairlie, 2007).

8.44 Recently, the Canadian Nuclear Safety Commission (CNSC, 2010) published the results of a review of the health effects of tritium exposure. In considering epidemiological studies, the report noted the findings of a study of childhood leukaemia incidence around nuclear facilities in Ontario (McLaughlin et al, 1993), which did not find statistically significantly different rates from those expected. Interestingly, tritium discharges from the heavy-water moderated reactors in Canada tend to be greater than those from the light-water moderated NPPs in operation throughout most of Europe, including Germany – therefore, if the risk of tritium-induced childhood leukaemia has been seriously underestimated, it might be expected to be apparent near Canadian nuclear facilities.

8.45 Both tritium and carbon-14 are naturally occurring radionuclides, but they were also produced as a result of atmospheric nuclear weapons testing, particularly during the late 1950s and early 1960s. CERRIE examined the incidence rates of childhood leukaemia obtained from eight large-scale cancer registries established before 1960 to determine whether the release into the atmosphere during nuclear weapons testing of fission products and other radionuclides (such as the isotopes of plutonium) had a detectable effect upon the risk of childhood leukaemia (CERRIE, 2004). The range of radionuclides (including internal emitters) from weapons testing fallout is similar to that resulting from nuclear installation discharges and would be expected to result in similar exposures. Therefore if the risk from radioactive discharges from NPPs has been significantly underestimated, it should also be apparent in the childhood leukaemia rates obtained from the eight registries following the peak of atmospheric nuclear weapons testing; however, no discernible increase in incidence was found. This provides strong evidence against an under-estimation of the risk of internal emitters of the degree required to explain the raised rates of childhood leukaemia found near some nuclear installations in terms of these radionuclides.

8.46 The study of the potential impact of internal emitters in the debris of nuclear weapons testing upon the risk of childhood leukaemia has recently been extended by Wakeford et al (2010). In particular, the authors examined the temporal trends of leukaemia in the 0–4 year age group in ten cancer registries from around the world. They found no discernible increase in the incidence of leukaemia in young children that could be attributed to fallout from atmospheric nuclear weapons testing, strengthening the evidence against an underestimation of risk. Since tritium and carbon-14 were produced in atmospheric nuclear weapons testing and generated doses comparable to, or greater than, those received from discharges from German NPPs, the absence of evidence from atmospheric nuclear weapons testing fallout of an underestimation of the risk of childhood leukaemia from these radionuclides points strongly away from discharges as an explanation for the KiKK study findings.

Summary

8.47 The four countries studied here – the United Kingdom, France, Germany and Switzerland – have varying numbers of NPPs, with different types of nuclear power reactors operating during the years considered. The typical composition and quantities of radionuclide discharges vary considerably with reactor type. In any comparison between countries of doses to the general public associated with radionuclide discharges, it is necessary to consider other variables, such as the geographical situation of the NPP, the age of the reactor and the reporting specifications.

8.48 Taking 1999 as an example year, the quantities of specific radionuclides discharged vary considerably between countries and between individual NPPs within each country. This variation may, in part, be due to discrepancies in reporting and differences in measuring practices. The requirements for reporting specific radionuclide discharges were not consistent across European countries in the selected year. It was not until 2004 that the European Commission issued its recommendation on standardised information on radioactive airborne and liquid discharges into the environment from nuclear installations. The Commission still does not require the reporting of liquid carbon-14 discharges from NPPs.

8.49 The general public is exposed to radioactivity from a variety of sources and an annual average effective dose is calculated based on both natural and man-made sources of ionising radiation. Doses from radioactive discharges from NPPs contribute to the man-made fraction of radiation exposure, together

with medical exposures. The average annual effective dose resulting from discharges from the nuclear industry in the UK can be estimated as around 0.0065% of the average annual effective dose from natural and medical exposures, based on 2005 figures.

8.50 A range of implied effective doses to a representative critical group has been determined from gaseous and liquid discharges for the UK, France and Germany for 1999. The doses are not solely related to distance but are assessed using the habits of the local population and incorporating meteorological and environmental factors. The calculations for implied doses from both gaseous and liquid discharges are reliant upon the availability of accurate and complete discharge records and, as a result, the values should be taken only as an indication of the dose received. The effective doses associated with radionuclide discharges from NPPs for 1999 for all three countries were estimated to be substantially below the 1 mSv limit for the general public and the annual average effective dose from natural radiation sources for each country. The discharges from the nuclear sector recorded in 2009 for the UK continue to be lower than in the past, which will in turn result in decreased doses to the general population.

8.51 A suggestion has been made that there is a substantial underestimation of the risk of childhood cancers from the intake of radionuclides and that discharges of tritium and carbon-14 may be responsible, in part, through *in utero* exposure of embryos and foetuses. Evidence presented to date does not support this suggestion.

CHAPTER 9

CONCLUSIONS

9.1 In this report, COMARE has reviewed the evidence from a variety of studies undertaken in a number of countries, using different methodologies, to determine whether there is an increased risk of childhood leukaemia in the vicinity of nuclear power plants (NPPs) as well as presenting a new geographical data analysis for Great Britain. It has also considered additional factors, which may have influenced the study results, including the status of cancer registries, the types of reactors used in the various countries, and the associated radionuclide discharges and doses to the general public from these discharges and other sources of exposure.

9.2 When considering the different methods of epidemiological analysis it should be recognised that each kind of study has strengths and weaknesses, which depend substantially on the details of the design and the area of application. As childhood leukaemia is a rare disease, the sample numbers in epidemiological studies are frequently small. For example, the KiKK case–control study in Germany included only 37 cases of leukaemia in children under 5 years of age, living within 5 km of an NPP over the 23 year period of the study (Kaatsch et al, 2008a; Spix et al, 2008), and the new analysis for Great Britain presented in this report had 20 observed cases (under 5 years of age, living within 5 km of an NPP) over the 35 years of the study.

9.3 Previous geographical studies in Great Britain, including that described in our tenth report, showed no significantly increased risks of childhood cancer, or in particular childhood leukaemia and non-Hodgkin lymphoma (NHL), within 25 km of an NPP, or any significantly increasing trend in incidence with proximity to an NPP. A further analysis of British data, specific to leukaemia and NHL incidence rates among children aged 0–4 years living within a 5 km radius of an NPP between 1969 and 2004, showed no significant increase in risk (Bithell et al, 2008, 2010). Studies in other countries, such as in France and Finland, also reported no general increase in childhood leukaemia or childhood cancer incidence near NPPs.

9.4 For the new British geographical study presented in this report, the primary analysis shows no statistically significant evidence of an association between leukaemia risk and proximity to an NPP in Great Britain in children under 5 years of age. It is therefore possible to conclude that, in spite of its limitations, the geographical analysis of British data is suggestive of a risk estimate for childhood leukaemia associated with proximity to an NPP that is extremely small, if not actually zero.

9.5 The KiKK case–control study in Germany concluded that there is evidence of a raised risk of leukaemia in children under 5 years of age living within 5 km of an NPP during 1980–2003, but not for distances greater than 5 km. The results were confirmed by an independent analysis of the data. Cases identified in earlier German investigations heavily influence the findings of the KiKK study (for the time periods 1980–1990 and 1991–1995). The more recent data (for the period 1996–2003) provide less evidence of an increased risk.

9.6 A marked excess incidence of childhood leukaemia has been found in the neighbourhood of the Krümmel NPP in northern Germany. The Krümmel cluster started in 1990 and continued until at least 2005, so its influence on the KiKK study results must be taken into account. For 1991–1995 and 1996–2003, the evidence for an increased risk of leukaemia in young children living within 5 km of German NPPs excluding Krümmel is only weak. The Northern Germany Leukaemia and Lymphoma (NLL) study could not explain the Krümmel cluster in terms of routine radioactive discharges.

9.7 There is a disparity in the leukaemia risk levels for the period 1980–1990 assessed by geographical studies and the KiKK case–control study. Possibilities for this difference include the distance measurements used and control selection in the KiKK study. Further investigation is required to understand this peculiarity – in particular because in the absence of the Krümmel data, the data for 1980–1990 are influential in generating the KiKK study findings.

9.8 Both British and German studies have considered the risk of leukaemia around potential nuclear sites (locations selected for an NPP but where construction was never undertaken) and found similar risk levels in some sites to those around active nuclear installations. This is suggestive of a risk associated with factors other than the operation of the plant, such as the nature of the location itself.

9.9 The risk of childhood leukaemia associated with living in the vicinity of NPPs has also been studied using meta-analyses. Such analyses can be seen as a powerful way of integrating the evidence from the results of a large number of smaller studies; however, methodological differences may severely limit their usefulness in practice. There are concerns with the treatment of heterogeneity and the selection criteria used in two reported meta-analyses (Baker and Hoel, 2007; Greiser, 2009). Further, the inclusion of nuclear installations other than those with a primary power generating function means that the relevance of these studies to NPPs is substantially constrained. Careful selection of the studies included and judicious adjustment of the parameters analysed, such as the time period studied, the type of cancer and the distance from the NPP, may permit the identification of 'statistically significant' results. It is also possible that the studies available for inclusion in a meta-analysis may be subject to 'publication bias'.

9.10 Childhood leukaemia is not a single, homogeneous disease and both acute lymphoblastic leukaemia (ALL) and acute myeloid leukaemia (AML) have definable subtypes. Although it may not be possible currently to establish the cause of an individual child's leukaemia, evidence suggests that factors other than radiation (including the existence of predisposing and spontaneously occurring genetic mutations and an abnormal immune response) are likely to be important in many cases.

9.11 Substantial evidence has been published in the past two decades indicating that patterns of infection are important in determining the risk of childhood leukaemia. The geographical distribution of cases throughout Great Britain found in the eleventh COMARE report is consistent with this evidence (COMARE, 2006). It is plausible that unusual infectious processes of relevance to the risk of childhood leukaemia have occurred in the vicinities of some nuclear installations, increasing the risk there. However, the biological mechanism needs to be established before a definitive conclusion on the role of infection in the aetiology of childhood leukaemia can be drawn.

9.12 When considering the pathology of the cases of childhood leukaemia, the children with acute leukaemia living within 10 km of a British NPP at the time of diagnosis appear not to differ from a larger group of control patients resident over 50 km from an NPP, except for the relative paucity of T-cell and pre-B-cell ALL. The implications of the immunophenotypic disparity between cases and controls are not clear, but this finding should be considered in any further investigations.

9.13 Childhood cancer is much less common than adult cancer. For epidemiological analyses investigating incidence rates for childhood cancers, there is a requirement for a comprehensive childhood cancer registration system that maintains a high level of ascertainment. Cancer registration systems vary between countries, operating on either a regional or national basis. From the four countries selected for detailed consideration in Chapter 7 (the United Kingdom, France, Germany and Switzerland), it is apparent that there are differences in the sources of cases, whether death certificates are used and the data collected. The UK is recognised as possessing one of the most comprehensive systems for cancer registration. The UK National Registry of Childhood Tumours (NRCT) is one of the longest running and largest cancer registries in the world. The comprehensive ascertainment of cases, the population base, and the collection and validation of a wide range of data items (including histological diagnosis, treatment and other clinical information) form the major strengths of the NRCT.

9.14 There are various types of nuclear reactors employed across the world for power generation. This report selected the UK*, France, Germany and Switzerland for detailed consideration, looking at the different numbers of NPPs in each country and the types of reactors employed. The typical composition and level of radionuclide discharges vary between reactor types; therefore as each country possesses a different selection of reactor types, the radionuclide discharges will also vary significantly. For comparison between countries, other variables also need to be taken into consideration, such as the geographical situation of the NPPs and the age of the reactors.

9.15 Considering the possibility that the radionuclide discharges from NPPs and the associated effective dose to members of the general public living in their vicinity may be a factor in the increased incidence of childhood leukaemia reported from some countries, COMARE investigated the levels of discharges and doses for the UK, France, Germany and Switzerland. Taking 1999 as an example year, the levels of discharges of specific radionuclides varied considerably between countries and between individual NPPs within each country. This variation may in part be due to discrepancies in reporting and differences in measuring practices. The requirement for reporting specific radionuclide discharges was not consistent across European countries in this selected year. The UK had the highest values of discharge levels for the radionuclides considered in this report. In each of the four countries, regulatory authorities assess the doses received by the public from the discharges of nuclear installations, and these are a small fraction of the overall radiation doses. In the UK, the measurement of radionuclides in food and the environment shows that doses to the general public from discharges from NPPs are well below the 1 mSv annual effective dose limit.

9.16 This report has also considered the implied radiation doses to the general public determined from gaseous and liquid discharge data for the UK, France and Germany for 1999 (EC, 2008). These doses are assessed using the habits of the local population as well as incorporating meteorological and

* It should be noted that although the reports considered in Chapter 8 refer to the United Kingdom, there are no nuclear reactors in Northern Ireland.

geographical factors and are therefore not solely related to distance from an NPP. Doses from liquid discharges also depend on the destination of the discharge. The calculations are reliant upon the availability of accurate discharge records, and the levels reported to the European Commission do not necessarily constitute the complete discharge inventory, due to variations in the reporting requirements. The implied doses for 1999 for all three EU countries were estimated to be substantially below the annual effective dose limit of 1 mSv for the general public and the average annual effective dose from natural sources of radiation. It is estimated that, in the UK, the annual effective dose from discharges from the nuclear industry accounts for around 0.0065% of the average annual effective dose from natural and medical sources of exposure. In Germany, the Commission on Radiological Protection concluded that radiation exposures to residents in the vicinity of German NPPs are lower, 'by a factor of considerably more than 1000', than the level that could cause the raised risk of childhood leukaemia reported from the KiKK study (SSK, 2008).

9.17 Extensive investigation of the uncertainties in the risk of childhood leukaemia arising from the radionuclides discharged from nuclear installations has taken place since the first report of the Seascale childhood leukaemia cluster in 1983. Much of this work has been carried out as a result of COMARE recommendations in earlier reports. No aspect of this uncertainty in the risk assessments has been found to be approaching a level that could account for the reported increases in childhood leukaemia incidence in terms of radiation exposure.

9.18 It has also been proposed that there is a substantial underestimation of the risk of childhood cancers from the intake of radionuclides and that discharges of tritium and carbon-14 may be responsible, in part, through *in utero* exposure of embryos and foetuses. Evidence presented to date does not support this suggestion.

9.19 COMARE appreciates that there are a number of issues associated with this review that require further research, including establishing the biological mechanism for childhood leukaemia and the biokinetics of, and tissue responses to, internal emitters. COMARE has also recognised that basic radiobiological research underlies and supports both radiation protection issues and translational radiobiology and appreciates the importance of sustaining research in this field*. The effects of internal emitters and the determination of the impact of low dose radiation exposure are two areas that COMARE previously highlighted for continued research.

9.20 Based on the evidence presented in this review, COMARE sees no reason to change its previous advice to Government (as given in our tenth report – COMARE, 2005) that there is no evidence to support the view that there is an increased risk of childhood leukaemia and other cancers in the vicinity of NPPs in Great Britain.

* http://www.comare.org.uk/statements/RRS.htm (accessed December 2010).

CHAPTER 10

RECOMMENDATIONS

In this report, COMARE has reviewed in depth the available evidence from several countries operating nuclear power programmes, including Great Britain and Germany, which have been the subject of major recent studies with apparently conflicting findings. We have also considered a current analysis for Great Britain, specific for risk of childhood leukaemia in children under 5 years of age living within 5 km of a nuclear power plant (NPP). Based on our review, we wish to make the following recommendations.

Recommendation 1

COMARE has found no reason to change its previous advice that there is no evidence to support the view that there is an increased risk of childhood leukaemia and other cancers in the vicinity of NPPs due to radiation effects. The Committee acknowledges, however, that it is almost impossible to come to a final conclusion on questions determined by epidemiological evidence alone, and also that circumstances relevant to risk change. In particular, operating practices need to be continually monitored and new possibilities for analysing the data may become available as recording and monitoring systems become more sophisticated. We therefore recommend that the Government keeps a watching brief in this area.

Recommendation 2

It is accepted that the creation of leukaemic cells is not a straightforward process. A variety of environmental factors have been proposed as causes of leukaemia and a number of hypotheses put forward on potential mechanisms for the process. Of growing importance is the role of infectious agents in the aetiology of childhood leukaemia. We reiterate recommendation 5 of our fourth report to continue initiatives into leukaemia and cancer research, both radiation and non-radiation related, to identify the causative mechanisms for childhood leukaemia.

Recommendation 3

Environmental and public health monitoring will be particularly important if the new nuclear build programme goes ahead. It is clear that the programme does not command universal support in the UK and therefore it is of considerable importance that any unfounded anxieties about health risks are properly addressed. We therefore strongly recommend that there is no reduction in the maintenance of effective surveillance, especially regarding the environment and the health of the population. This would include continuation of the programme of environmental measurements of radioactivity which, unlike the case in some other countries, permits an independent check on reported and measured discharges from British nuclear installations.

Recommendation 4

In the course of our investigations, it became clear that carbon-14, a radioactive isotope of carbon, is a significant contributor to the radiation doses which the public receive from discharges from NPPs. This radionuclide has not been specifically implicated in health risks to date. However, as a result of its contribution to public doses, we recommend that monitoring of carbon-14 discharges (both gaseous and liquid) remains a regulatory requirement for existing nuclear installations and is mandatory for any new NPPs in the UK. We also recommend that the requirement for monitoring of carbon-14 in the

liquid discharges of NPPs is extended to the rest of the European Union, if possible, to increase the consistency of monitoring radioactive discharges from nuclear installations.

Recommendation 5

COMARE acknowledges the possibility of further studies of British data that could be explored. The analyses of British data described in Chapter 6 of this report were carried out specifically at the Committee's request and used data from the National Registry of Childhood Tumours (NRCT), which is unequalled worldwide for the size and quality of its database. The analyses themselves were supported by the research programme of the Childhood Cancer Research Group (CCRG). This is part of the high quality cancer registration system in the UK, which provides the capability to carry out comprehensive epidemiological analyses of childhood cancer data. We therefore recommend that these and other UK-wide resources, which allow such studies to be carried out in both children and adults, should continue to be specifically supported. We also reiterate recommendation 6 of our eleventh report regarding the processes and procedures involved in data collection for this registration system.

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THE APPENDICES

APPENDIX A

GLOSSARY AND SELECTED ABBREVIATIONS

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 specific name gray (Gy), where 1 Gy = 1 joule per kg.

AETIOLOGY — The study of causes of disease.

ALL — *See **LEUKAEMIA.***

AML — *See **LEUKAEMIA.***

ATMOSPHERIC PRESSURE — Force per unit area exerted by the air above the surface of the Earth. Standard sea-level pressure, by definition, equals one atmosphere (atm), but pressure varies with elevation and temperature.

BACKGROUND RADIATION — Radiation that comes from naturally occurring radioactive material in the ground and from cosmic rays irradiating the Earth from outer space. The UK average dose from background radiation is 2.2 millisievert (mSv) per year: regional averages range from 1.5–7.5 mSv per year.

BECQUEREL (Bq) — A unit of radiation equal to one disintegration per second. Discharges are normally expressed in:

Megabecquerels (MBq) – one million Bq

Gigabecquerels (GBq) – one thousand million Bq

Terabecquerels (TBq) – one million million Bq

CARCINOMA — A malignant tumour that may spread to surrounding tissue and distant areas of the body.

CASE–CONTROL STUDY — A study in which the risk factors for a group of individuals identified as having the disease, the *cases*, are compared to those for a group of individuals not having the disease, the *controls*.

CENSUS — The enumeration of an entire population, usually with details being recorded on residence, age, sex, occupation, ethnic group, marital status, birth history, and relationship to head of household.

CLL — *See **LEUKAEMIA.***

CLUSTERING — The irregular grouping of cases of disease in time (where cases of a particular disease which might normally occur at a fairly constant rate in a community appear with unduly high frequency in a certain time period); space (where cases of a particular disease occurring within a certain time period tend to cluster in a well-defined location); or in both time and space (where cases that occurred close together in space would tend also to be close in time, eg in the aetiology of some rare diseases such as leukaemia).

COHORT STUDY A study design used in analytical epidemiology. Cohort studies are designed to answer the question, 'What are the effects of a particular exposure?' They compare a group of individuals 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.

COLLECTIVE DOSE Collective dose is a measure of the total amount of effective dose multiplied by the size of the exposed population. Collective dose is usually measured in units of person-sievert or man-sievert.

CONFIDENCE INTERVAL (CI) An interval calculated from the data to indicate the (im)precision of an estimate of some parameter, eg the risk of a disease. A CI conveys the effect of sampling variation on the precision of the estimate. Specifically, the true rate will lie inside a 95% CI on 95% of occasions. This 'confidence coefficient' is often chosen to be 95%, although this is entirely arbitrary.

CONFIDENCE LIMIT (CL) A quantity calculated from the data to indicate a limit below (or above) which a parameter is unlikely to lie, in the sense that in a stated proportion of such calculations (say 97.5%), the calculated limit will be less (or greater) than the true value. Two such limits form a (95%) *confidence interval*.

CONFOUNDING Confounding is a problem in epidemiological studies which arises when there is a factor associated with both the exposure being investigated and the disease under study. This can give rise to an apparent relationship between the factor being investigated and the disease, even though the factor did not cause the disease. For example, suppose lung cancer was being studied in workers exposed 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.

DECOMMISSIONING Removal of a facility (eg reactor) from service.

EFFECTIVE DOSE Effective dose is a measure of dose in which the type of radiation and the sensitivity of tissues and organs to that radiation is taken into account. The probability of a harmful effect from radiation exposure depends on what part or parts of the body are exposed. A tissue weighting factor (w_T) is used to take this into account. The unit of effective dose is the sievert (Sv).

EFFLUENT A discharge of liquid waste, as from a factory or nuclear plant.

EPIDEMIOLOGY The study of factors affecting health and illness of populations, regarding the causes, distribution and control.

FISSILE (Of an isotope) capable of capturing a neutron and undergoing nuclear fission.

FISSION The splitting of a heavy nucleus into two, accompanied by the release of a relatively large amount of energy and generally one or more neutrons. It may be spontaneous but is usually due to a nucleus absorbing a neutron.

GEO-CODE The demographic characterisation of a neighbourhood or locality.

GEOGRAPHICAL (ECOLOGICAL) STUDY An epidemiological study in which the frequency of disease (or death) is observed in different areas and the locations of these areas are then related to putative sources of risk of the disease. In effect, the location and other attributes of the area are imputed to the cases without any possibility of distinguishing between them.

GRAY (Gy) The international (SI) unit of absorbed dose: one gray is equivalent to one joule of energy absorbed per kilogram of matter such as body tissue.

HAEMATOLOGY The branch of medical science concerned with diseases of the blood and blood-forming tissues.

HAZARD A property that in particular circumstances could lead to harm, eg exposure to radiation leading to damage to an individual's health.

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', ie the number of cases divided by the (average) number at risk in the relevant time period.

INTRACRANIAL Within the skull.

INTRASPINAL Situated within, occurring within, or introduced into the spinal column and especially the vertebral canal.

LANGERHANS CELL HISTIOCYTOSIS (LCH) A rare disease involving clonal proliferation of Langerhans cells, abnormal cells deriving from bone marrow and capable of migrating from skin to lymph nodes. Clinically, its manifestations range from isolated bone lesions to multi-system disease.

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 can be classified as lymphoid or myeloid and as either acute or chronic (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.

Acute lymphoblastic leukaemia (ALL) is subdivided into three types using the French-American-British classification of:

- **L1** Small monotonous lymphocytes
- **L2** Mixed L1- and L3-type lymphocytes
- **L3** Large homogeneous blast cells

Each subtype can be further classified by immunophenotyping, with two main immunological types: pre-B-cell and pre-T-cell. The mature B-cell ALL (L3) is now classified as Burkitt's lymphoma/leukaemia. Subtyping helps determine the prognosis and most appropriate treatment for ALL.

LINEAR RISK SCORE A test statistic designed to determine whether a group of cases are closer to a particular point (such as a nuclear power plant) than would be expected given the population distribution in the area. It simply scores each case with a suitable measure of proximity, such as the reciprocal of distance, and adds the scores over all cases, comparing this with the value that would be expected for a random sample from the population.

LYMPHOMA A malignant tumour of the lymphatic system (lymph nodes, reticuloendothelial system and lymphocytes).

MALIGNANT Synonymous with cancerous. Malignant neoplasms or tumours can invade and destroy other tissues and spread to other parts of the body via the bloodstream or lymphatics (metastasis).

MEGAWATT (MW) A unit of power (10^6 watts). MWe refers to the electrical output of a generator; MWt to the thermal output from a reactor or heat source.

META-ANALYSIS A statistical analysis used to combine the results of several studies addressing a set of related research hypotheses, usually conducted to pool findings and incorporate information from small studies with low power. It can test whether the study outcomes show more variation than expected owing to population differences and different study designs.

MONOTONIC Consistently increasing or decreasing in value.

MYELODYSPLASIA Disorders of myeloid cells of the bone marrow, either in number or degree of maturity.

NEOPLASM An abnormal growth of tissue in animals or plants, such as a tumour. Neoplasms can be benign or malignant.

NEUTRON An uncharged subatomic elementary particle. Solitary mobile neutrons travelling at various speeds originate from fission reactions.

NOBLE GASES Any of the six gases helium, neon, argon, krypton, xenon and radon, that do not react chemically with other substances except under certain special conditions. Also called inert gases.

NON-HODGKIN LYMPHOMA (NHL) A group of lymphomas that differ in important ways from Hodgkin lymphoma 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.

NON-PARAMETRIC No assumptions are made about the population from which the data are drawn.

NUCLEAR REACTOR An engineering construction in which a nuclear fission chain reaction occurs under controlled conditions so that the heat yielded may be harnessed or the neutron beam utilised.

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 an event occurring in one group to the odds of it occurring in another group.

ONCOLOGY The branch of medicine that deals with tumours, including study of their development, diagnosis, treatment and prevention.

P-VALUE The probability that, under a given null hypothesis, a particular test statistic would have, purely by chance, a value at least as disparate with the hypothesis as that observed. 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. For a significance test at the 5% level, 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. Its interpretation depends on the plausibility of available alternative hypotheses or explanations.

PAEDIATRIC Of or relating to the medical care of children.

POISSON DISTRIBUTION The Poisson distribution is a probability distribution describing the numbers of events happening independently of one another, eg the number of cancers within an area. The mean and variance of counts that follow the Poisson distribution are equal.

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 supposedly prompted 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.

PROBABILITY A measure of how likely an unpredictable event is to occur on a given occasion. Mathematically it is measured on a scale of zero to one, which may be expressed as a percentage. Its usefulness in statistics stems from the fact that it can be estimated from the proportion of corresponding outcomes in repetitions of the same experimental or observational situation, and this estimation becomes more precise as the number of repetitions increases.

RADIATION The emission and propagation of energy by means of rays or waves or sub-atomic particles.

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).

RECALL BIAS A source of bias due to differential recall by cases and controls. In many case–control studies retrospective information is obtained by interviewing the subjects or their relatives. People with a particular disease or condition may have thought a lot about a possible link with past events, especially with respect to widely publicised risk factors. Their recall of past events may consequently differ from that of people without the disease or condition under study.

REGRESSION COEFFICIENT The slope of the straight line that most closely relates two correlated variables.

RELATIVE RISK (RR) A ratio of the risk of disease or death among those exposed to a potential hazard to the risk among those not exposed to the hazard.

RETINOBLASTOMA A common childhood malignancy of the eye that develops from retinal cells.

RISK A combination of the probability, or frequency, of occurrence of a defined hazard and the magnitude of the consequences of the occurrence. *See **HAZARD** and **RELATIVE RISK.***

Risk is sometimes taken to mean the probability that an event will occur, eg that an individual will become ill or die within a stated period of time or age. Risk is also used as a non-technical term encompassing a variety of measures of the probability of a (generally) unfavourable outcome.

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 millisievert (mSv) – ie one-thousandth of one sievert. The average annual effective radiation dose received by members of the public in the UK is around 2.7 mSv.

SIGNIFICANCE TEST	A formal procedure for assessing the evidence against a null hypothesis, specified in advance. The formal version results either in rejection of the null hypothesis in favour of some alternative, or in its acceptance. A test is associated with a 'significance level', which is the probability that this rejection would occur by chance when the null hypothesis is true. Typically this significance level is chosen to be 5%, but the choice is entirely arbitrary. In a less formal version of the significance test a P-value is calculated. Data that result in the rejection of a hypothesis at a given significance level, or equivalently in a P-value less than such a level, are described as being 'statistically significant' at this level.
SOCIO-DEMOGRAPHIC	A population variable relating either to intrinsic properties of an area, such as population density, or to the average of some personal characteristic of the inhabitants, such as age, socioeconomic status or degree of household overcrowding.
SOCIOECONOMIC STATUS	A measure related to levels of living or social class. It may apply to individuals or groups. In this report it is applied to the populations of census wards or county districts, and is based on information from the 1981 census.
STANDARDISED INCIDENCE RATIO (SIR)	The ratio of the actual number of cases in a study group or population to the expected number. The expected number is calculated using the age- and sex-specific incidence rates for a reference population. These 'reference rates' will often be those of the national population but may also be taken from a smaller area.
STANDARDISED MORTALITY RATIO (SMR)	The standardised incidence ratio for the deaths in a study group or population.
TREND	The tendency for the values of a variable to increase or decrease as some other variable – most commonly time – changes.
URANIUM	A radioactive element with two isotopes which are fissile (uranium-233 and uranium-235). Uranium is the basic raw material of nuclear energy.

Selected abbreviations

EPIDEMIOLOGICAL TERMS	CI	Confidence interval
	CL	Confidence limit
	LRS	Linear risk score
	MLR	Maximum likelihood ratio
	OR	Odds ratio
	RR	Relative risk
	SES	Socioeconomic status
	SIR	Standardised incidence ratio
CANCER TYPES	ALL	Acute lymphoblastic leukaemia
	AML	Acute myeloid leukaemia
	LNHL	Leukaemia and non-Hodgkin lymphoma (collectively)
	ML	Myeloid leukaemia
	NHL	Non-Hodgkin lymphoma
REACTOR TYPES	AGR	Advanced gas cooled reactor
	GCR	Gas cooled reactor
	PWR	Pressurised water reactor
	BWR	Boiling water reactor
RADIONUCLIDES	Am	Americium
	C	Carbon
	Co	Cobalt
	Cs	Caesium
	I	Iodine
	Kr	Krypton
	Pu	Plutonium
	S	Sulphur
	Sr	Strontium
	U	Uranium
	Xe	Xenon

APPENDIX B

NUCLEAR REACTOR TYPES

Pressurised water reactor (PWR)

B1 The PWR is the most common type of reactor in the world, and its design originated as a submarine power plant. PWRs use ordinary water as both coolant and moderator. A PWR core has fuel clad in zircaloy, which contains enriched uranium (ie contains up to 4.9% more uranium-235 than the 0.7% found in natural uranium) – see Figure B1. Fuel assemblies are arranged vertically in the core, and a large reactor would have about 150–250 fuel assemblies with 80–100 tonnes of uranium. The design is distinguished by having a primary cooling circuit that facilitates the coolant to flow through the core of the reactor under high pressure, and heat is transferred to a secondary circuit which contains a steam generator; the steam drives a turbine to generate electricity.

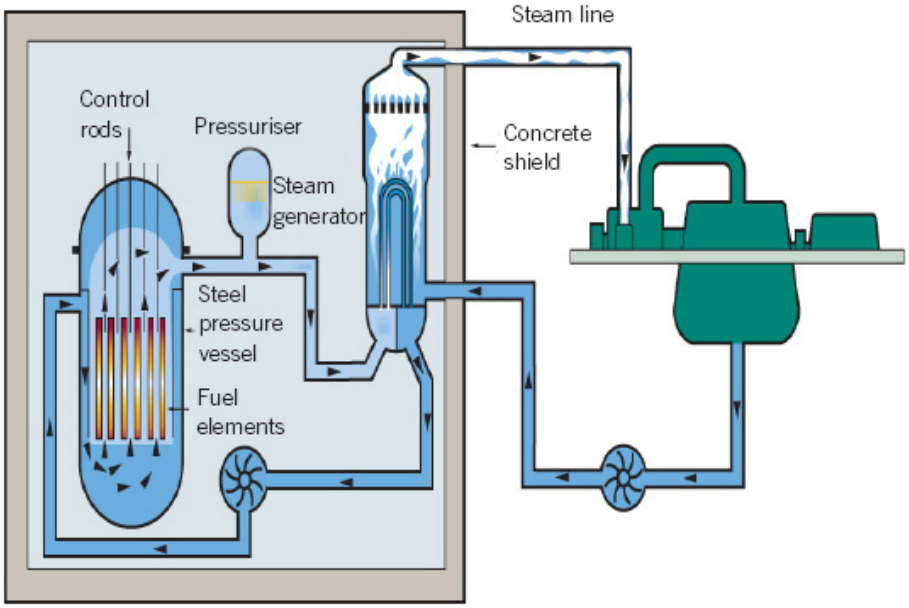

Figure B1 Pressurised water reactor (PWR) schematic

Source: Institution of Engineering and Technology

B2 Water in the reactor core reaches about 325°C; hence it must be kept under 150 times atmospheric pressure to prevent it from boiling. Pressure is maintained and controlled by a steam bubble in a pressuriser. In the primary cooling circuit the water is also the moderator, and if it turned to steam in the reactor core the fission reaction would slow down. This negative feedback effect is one of the safety features of PWRs. In addition to the provision of control rods, PWRs include a secondary shutdown system, which involves adding boron to the primary circuit.

Boiling water reactor (BWR)

B3 This design has similarities to the PWR, but there is only one circuit; the water boils in the reactor core and steam passes through separators and dryers above the core and then goes directly to the turbines (see Figure B2). The water pressure is lower than in a PWR (about 75 times atmospheric pressure) and it boils in the core at about 285°C. The reactor is designed to operate with 12–15% of the water in the top part of the core as steam, and hence with less moderating effect.

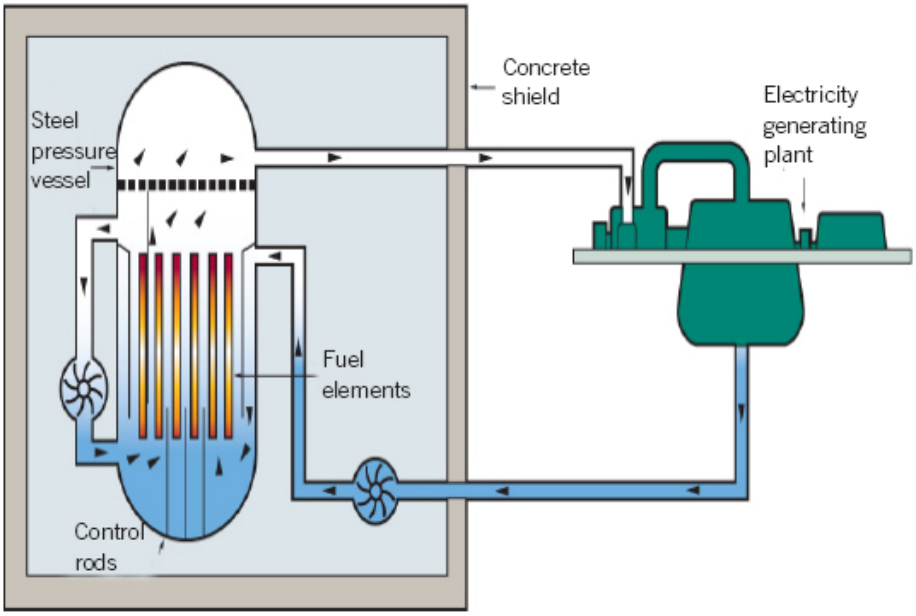

Figure B2 Boiling water reactor (BWR) schematic
Source: Institution of Engineering and Technology

B4 Since the water moving through the core of a reactor always becomes radioactive (activation and contamination) the turbine must be shielded and radiological protection provided during its maintenance. Most of the radioactivity in the water is very short-lived (notably nitrogen-16, with a 7 second half-life), so the turbine hall can be entered soon after the reactor is shut down.

B5 BWR fuel, up to 4.9% enriched uranium dioxide clad in zircaloy, is formed into assemblies comprising 90–100 fuel rods. There are up to 750 assemblies in a reactor core, holding up to 140 tonnes of uranium. The secondary control system involves restricting water flow through the core so that more steam in the top part reduces moderation.

Advanced gas cooled reactor (AGR)

B6 This is the second generation of British gas cooled reactors, using graphite as a moderator and carbon dioxide as a coolant (shown in Figure B3). The fuel is uranium oxide pellets, enriched to 2.5–3.5%, clad in stainless steel which is inserted into vertical channels in the graphite. The carbon dioxide circulates through the core, reaching temperatures of 650°C, past steam generator tubes outside the core, but still contained inside the concrete and steel pressure vessel. Control rods penetrate the moderator and a secondary shutdown system involves injecting nitrogen into the coolant.

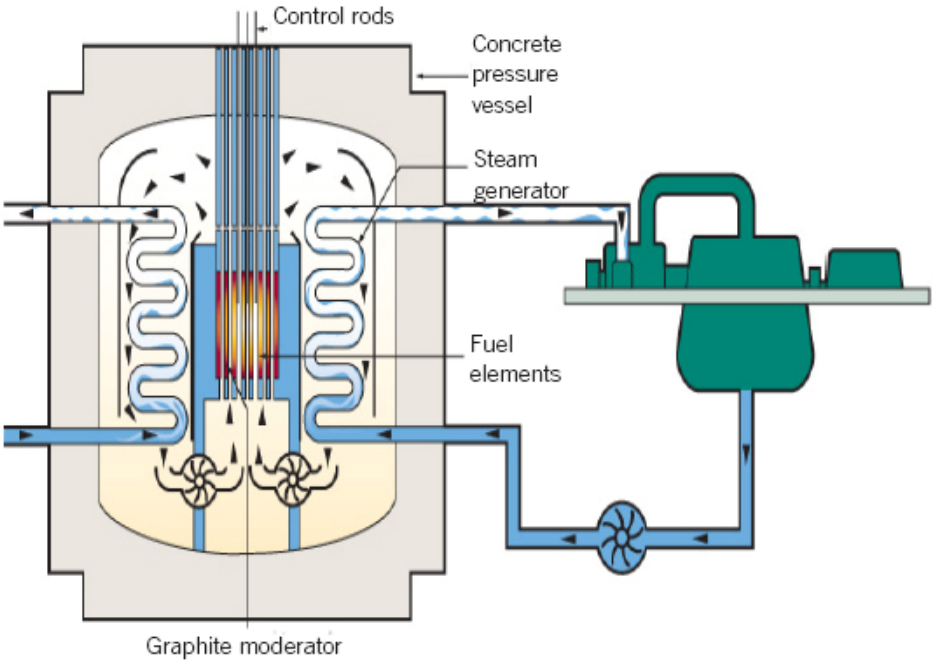

Figure B3 Advanced gas cooled reactor (AGR) schematic
Source: Institution of Engineering and Technology

Magnox reactor

B7 Magnox reactors (or gas cooled reactors, GCR) are the forerunners of the AGRs and also are graphite moderated and carbon dioxide cooled (see Figure B4). The two Magnox NPPs still operating in the UK have a reinforced concrete pressure vessel, and use natural uranium fuel in metal form clad in an alloy of magnesium (292 tonnes at Oldbury, 595 tonnes at Wylfa). The coolant temperature reaches only 350°C, making Magnox reactors less efficient than the more recently developed AGRs.

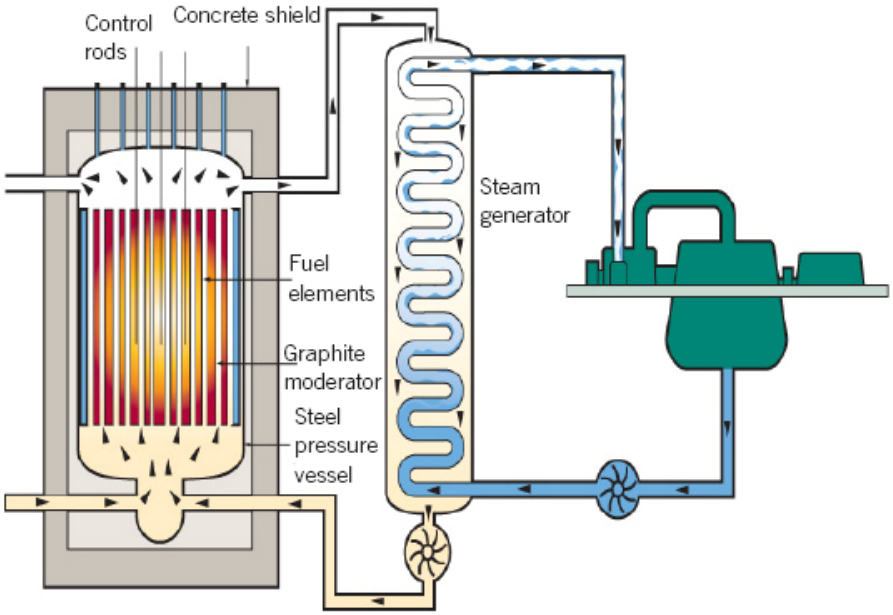

Figure B4 Basic gas cooled reactor (Magnox) schematic
Source: Institution of Engineering and Technology

APPENDIX C

NUCLEAR POWER PLANTS IN THE UK, FRANCE, GERMANY AND SWITZERLAND

Operational reactors are shown in bold

Reactor	Type	Net thermal power (MWe)	Discharges into	Operational from	Shut down
United Kingdom					
Berkeley	*2 GCR*	*276*	*Severn Estuary*	*1962*	*1989*
Bradwell	*2 GCR*	*246*	*North Sea*	*1962*	*2002*
Chapelcross	*4 GCR*	*240*	*Solway Firth*	*1959*	*2004*
Dungeness A	*2 GCR*	*450*	*English Channel*	*1965*	*2006*
Dungeness B	**2 AGR**	**1110**	**English Channel**	**1985**	
Hartlepool	**2 AGR**	**605**	**North Sea**	**1983**	
Heysham 1	**2 AGR**	**575**	**Morecambe Bay**	**1983**	
Heysham 2	**2 AGR**	**1250**	**Morecambe Bay**	**1989**	
Hinkley Point A	*2 GCR*	*470*	*Severn Estuary*	*1965*	*1999*
Hinkley Point B	**2 AGR**	**1220**	**Severn Estuary**	**1976**	
Hunterston A	*2 GCR*	*300*	*Firth of Clyde*	*1964*	*1990*
Hunterston B	**2 AGR**	**1190**	**Firth of Clyde**	**1976**	
Oldbury	**2 GCR**	**434**	**Severn Estuary**	**1967**	
Sizewell A	*2 GCR*	*420*	*North Sea*	*1966*	*2006*
Sizewell B	**1 PWR**	**1188**	**North Sea**	**1995**	
Torness	**2 AGR**	**1250**	**North Sea**	**1988**	
Trawsfynydd	*2 GCR*	*390*	*Trawsfynydd lake*	*1965*	*1993*
Wylfa	**2 GCR**	**950**	**Irish Sea**	**1971**	
France					
Belleville	**2 PWR**	**2620**	**Loire**	**1988**	
Bugey 2-5	**4 PWR**	**3640**	**Rhone**	**1978**	
Cattenom	**4 PWR**	**5200**	**Mosel**	**1987**	
Chinon	**4 PWR**	**3585**	**Loire**	**1984**	
Chooz	**2 PWR**	**2910**	**Meuse**	**2000**	
Civaux	**2 PWR**	**2910**	**Vienne**	**2002**	
Cruas	**4 PWR**	**3590**	**Rhone**	**1983**	
Dampierre en-Burly	**4 PWR**	**3560**	**Loire**	**1980**	
Fessenheim	**2 PWR**	**1760**	**Rhine**	**1977**	
Flamanville	**2 PWR**	**2660**	**English Channel**	**1986**	
Golfech	**2 PWR**	**2620**	**Garonne**	**1991**	
Gravelines	**6 PWR**	**5460**	**North Sea**	**1980**	
Le Blayais	**4 PWR**	**3640**	**Gironde Estuary**	**1981**	

Reactor	Type	Net thermal power (MWe)	Discharges into	Operational from	Shut down
France *(continued)*					
Nogent-sur-Seine	**2 PWR**	**2620**	**Seine**	**1988**	
Paluel	**4 PWR**	**5320**	**English Channel**	**1985**	
Penly	**2 PWR**	**2660**	**English Channel**	**1990**	
Saint Alban	**2 PWR**	**2670**	**Rhone**	**1986**	
Saint Laurent	**2 PWR**	**1795**	**Loire**	**1983**	
Tricastin	**4 PWR**	**3660**	**Rhone**	**1980**	
Germany					
Biblis A	**1 PWR**	**1176**	**Rhine**	**1975**	
Biblis B	**1 PWR**	**1240**	**Rhine**	**1977**	
Brokdorf	**1 PWR**	**1326**	**Elbe**	**1986**	
Brunsbüttel	**1 BWR**	**771**	**Elbe**	**1977**	
Grafenrheinfeld	**1 PWR**	**1275**	**Main**	**1982**	
Grohnde/Emmerthal	**1 PWR**	**1360**	**Weser**	**1985**	
Gundremmingen-B	**1 BWR**	**1284**	**Danube**	**1984**	
Gundremmingen-C	**1 BWR**	**1288**	**Danube**	**1985**	
Isar 1	**1 BWR**	**870**	**Danube**	**1979**	
Isar 2	**1 PWR**	**1400**	**Danube**	**1988**	
Kahl	*1 BWR*	*15*	*Main*	*1970*	*1985*
Krümmel/Geesthacht	**1 BWR**	**1260**	**Elbe**	**1984**	
Lingen/Emsland	**1 PWR**	**1290**	**Ems**	**1988**	
Lingen	*1 BWR*	*250*	*Ems*	*1970*	*1979*
Mülheim-Kärlich	*1 PWR*	*1219*	*Rhine*	*1986*	*1988*
Neckar-westheim 1	**1 PWR**	**785**	**Neckar**	**1976**	
Neckar-westheim 2	**1 PWR**	**1269**	**Neckar**	**1989**	
Obrigheim	*1 PWR*	*340*	*Neckar*	*1968*	*2005*
Philippsburg KKP1	**1 BWR**	**890**	**Rhine**	**1980**	
Philippsburg KKP2	**1 PWR**	**1358**	**Rhine**	**1985**	
Rheinsberg	*1 PWR*	*70*	*Havel*	*1966*	*1990*
Stade	*1 PWR*	*640*	*Elbe*	*1972*	*2003*
Rodenkirchen-Unterweser	**1 PWR**	**1285**	**Weser**	**1979**	
Würgassen/Beverungen	*1 BWR*	*640*	*Weser*	*1971*	*1994*
Switzerland					
Beznau	**2 PWR**	**700**	**Aare**	**1970**	
Gösgen	**1 PWR**	**940**	**Aare**	**1979**	
Leibstadt	**1 BWR**	**990**	**Rhine**	**1984**	
Mühleberg	**1 BWR**	**355**	**Aare**	**1971**	

APPENDIX D

SPECIFIC RADIONUCLIDE DISCHARGES REPORTED FROM NUCLEAR POWER PLANTS FOR 1999–2001

Gaseous discharges

	Gaseous discharges (TBq)											
	Tritium			Carbon-14			Cobalt-60			Caesium-137		
Reactor	1999	2000	2001	1999	2000	2001	1999	2000	2001	1999	2000	2001
United Kingdom												
Berkeley	$4.0\ 10^{-3}$	$4.8\ 10^{-3}$	$4.2\ 10^{-3}$	$1.2\ 10^{-4}$	$1.9\ 10^{-4}$	$2.0\ 10^{-4}$	–	–	–	–	–	–
Bradwell	$7.8\ 10^{-1}$	$6.4\ 10^{-1}$	$9.0\ 10^{-1}$	$2.0\ 10^{-1}$	$2.0\ 10^{-1}$	$4.6\ 10^{-1}$	$2.3\ 10^{-4}$	$2.0\ 10^{-4}$	$3.3\ 10^{-4}$	–	–	–
Chapelcross	$1.4\ 10^{3}$	$1.5\ 10^{3}$	$8.4\ 10^{2}$	–	–	–	–	–	–	–	–	–
Dungeness A	$5.1\ 10^{-1}$	$5.5\ 10^{-1}$	$6.9\ 10^{-1}$	$3.6\ 10^{0}$	$3.3\ 10^{0}$	$3.0\ 10^{0}$	$3.1\ 10^{-4}$	$2.4\ 10^{-4}$	$2.2\ 10^{-4}$	–	–	–
Dungeness B	$1.2\ 10^{0}$	$2.7\ 10^{0}$	$8.1\ 10^{-1}$	$4.7\ 10^{-1}$	$2.8\ 10^{-1}$	$5.2\ 10^{-1}$	–	–	–	–	–	–
Hartlepool	$1.6\ 10^{0}$	$1.9\ 10^{0}$	$1.8\ 10^{0}$	$1.7\ 10^{0}$	$1.5\ 10^{0}$	$2.1\ 10^{0}$	–	–	–	–	–	–
Heysham 1	$1.1\ 10^{0}$	$9.5\ 10^{-1}$	$1.4\ 10^{0}$	$6.9\ 10^{-1}$	$1.4\ 10^{0}$	$1.2\ 10^{0}$	–	–	–	–	–	–
Heysham 2	$1.2\ 10^{0}$	$1.1\ 10^{0}$	$1.7\ 10^{0}$	$1.1\ 10^{0}$	$9.4\ 10^{-1}$	$1.2\ 10^{0}$	–	–	–	–	–	–
Hinkley Point A	$3.3\ 10^{0}$	$7.9\ 10^{-2}$	$6.3\ 10^{-1}$	–	$5.6\ 10^{-2}$	$2.1\ 10^{-3}$	$5.0\ 10^{-5}$	$1.2\ 10^{-6}$	$2.2\ 10^{-6}$	–	–	–
Hinkley Point B	$2.2\ 10^{0}$	$3.1\ 10^{0}$	$5.0\ 10^{0}$	$1.2\ 10^{0}$	$1.0\ 10^{0}$	$1.1\ 10^{0}$	–	–	–	–	–	–
Hunterston A	Nil	Nil	Nil	Nil	Nil	Nil	$4.7\ 10^{-7}$	$4.6\ 10^{-7}$	$3.6\ 10^{-7}$	–	–	–
Hunterston B	$3.5\ 10^{0}$	$5.7\ 10^{0}$	$7.3\ 10^{0}$	$2.0\ 10^{0}$	$1.8\ 10^{0}$	$1.9\ 10^{0}$	–	–	–	–	–	–
Oldbury	$2.4\ 10^{0}$	$1.6\ 10^{0}$	$2.1\ 10^{0}$	$3.9\ 10^{0}$	$4.0\ 10^{0}$	$4.7\ 10^{0}$	$1.1\ 10^{-4}$	$1.1\ 10^{-4}$	$1.4\ 10^{-4}$	–	–	–
Sizewell A	$1.4\ 10^{0}$	$9.2\ 10^{-1}$	$2.1\ 10^{0}$	$1.1\ 10^{0}$	$1.1\ 10^{0}$	$1.0\ 10^{0}$	$1.5\ 10^{-4}$	$1.8\ 10^{-4}$	$1.9\ 10^{-4}$	–	–	–
Sizewell B	$6.9\ 10^{-1}$	$5.7\ 10^{-1}$	$1.8\ 10^{0}$	$2.3\ 10^{-2}$	$1.8\ 10^{-1}$	$1.8\ 10^{-1}$	–	–	–	–	–	–
Torness	$1.3\ 10^{0}$	$1.7\ 10^{0}$	$2.4\ 10^{0}$	$5.8\ 10^{-1}$	$5.8\ 10^{-1}$	$5.6\ 10^{-1}$	–	–	–	–	–	–
Trawsfynydd	$9.3\ 10^{-2}$	$1.7\ 10^{-1}$	$1.1\ 10^{-1}$	$8.8\ 10^{-4}$	$1.2\ 10^{-3}$	$2.9\ 10^{-3}$	$2.1\ 10^{-6}$	$1.6\ 10^{-6}$	$1.8\ 10^{-6}$	–	–	–
Wylfa	$4.8\ 10^{0}$	$6.0\ 10^{0}$	$1.6\ 10^{0}$	$1.5\ 10^{0}$	$5.2\ 10^{-1}$	$4.0\ 10^{-1}$	$7.8\ 10^{-5}$	$9.6\ 10^{-5}$	$2.3\ 10^{-5}$	–	–	–
France												
Belleville	$1.9\ 10^{0}$	$1.9\ 10^{0}$	$2.0\ 10^{0}$	–	–	$4.3\ 10^{-1}$	–	–	–	–	–	–
Cattenom	$1.1\ 10^{0}$	$1.7\ 10^{0}$	$2.6\ 10^{0}$	–	–	–	–	–	–	–	–	–
Chinon	$1.2\ 10^{0}$	$1.1\ 10^{0}$	$1.1\ 10^{0}$	–	–	–	–	–	–	–	–	–
Chooz	$6.7\ 10^{-1}$	$5.2\ 10^{-1}$	$3.2\ 10^{-1}$	–	–	–	–	–	–	–	–	–
Civaux	$2.4\ 10^{-2}$	$1.3\ 10^{-1}$	$1.9\ 10^{-1}$	–	–	–	–	–	–	–	–	–
Dampierre en-Burly	$7.4\ 10^{-1}$	$6.0\ 10^{-1}$	$6.9\ 10^{-1}$	–	–	–	–	–	–	–	–	–
Fessenheim	$4.4\ 10^{-1}$	$4.7\ 10^{-1}$	$5.3\ 10^{-1}$	–	–	–	–	–	–	–	–	–
Flamanville	$2.4\ 10^{0}$	$3.6\ 10^{0}$	$2.7\ 10^{0}$	–	–	$7.0\ 10^{-1}$	–	–	–	–	–	–
Golfech	$2.5\ 10^{0}$	$3.1\ 10^{0}$	$2.9\ 10^{0}$	–	–	–	–	–	–	–	–	–
Gravelines	$2.4\ 10^{0}$	$2.4\ 10^{0}$	$2.2\ 10^{0}$	–	–	–	–	–	–	–	–	–
Le Blayais	$4.4\ 10^{-1}$	$5.7\ 10^{-1}$	$4.8\ 10^{-1}$	–	–	–	–	–	–	–	–	–
Nogent-sur-Seine	$1.7\ 10^{0}$	$1.6\ 10^{0}$	$1.7\ 10^{0}$	–	–	–	–	–	–	–	–	–
Paluel	$2.3\ 10^{0}$	$3.3\ 10^{0}$	$2.8\ 10^{0}$	–	–	$8.7\ 10^{-1}$	–	–	–	–	–	–
Penly	$2.3\ 10^{0}$	$2.9\ 10^{0}$	$2.7\ 10^{0}$	–	–	–	–	–	–	–	–	–
Saint Laurent	$5.0\ 10^{-1}$	$4.4\ 10^{-1}$	$4.6\ 10^{-1}$	–	$2.5\ 10^{-1}$	$3.3\ 10^{-1}$	–	–	–	–	–	–

Reactor	Gaseous discharges (TBq)											
	Tritium			Carbon-14			Cobalt-60			Caesium-137		
	1999	2000	2001	1999	2000	2001	1999	2000	2001	1999	2000	2001
Germany												
Biblis A	$2.4\ 10^{-1}$	$5.1\ 10^{-1}$	$1.5\ 10^{-1}$	$3.0\ 10^{-1}$	$3.7\ 10^{-1}$	$7.4\ 10^{-2}$	$5.7\ 10^{-7}$	–	$2.6\ 10^{-8}$	–	$4.0\ 10^{-8}$	–
Biblis B	$1.8\ 10^{-1}$	$2.7\ 10^{-1}$	$2.1\ 10^{-1}$	$1.0\ 10^{-1}$	$4.0\ 10^{-1}$	$1.6\ 10^{-1}$	$5.2\ 10^{-7}$	$3.1\ 10^{-7}$	$7.0\ 10^{-8}$	$6.1\ 10^{-9}$	–	–
Brokdorf	$3.2\ 10^{-1}$	$3.8\ 10^{-1}$	$3.6\ 10^{-1}$	$3.0\ 10^{-1}$	$3.7\ 10^{-1}$	$2.8\ 10^{-1}$	–	$2.1\ 10^{-6}$	–	–	–	–
Brunsbüttel	$7.5\ 10^{-2}$	$8.1\ 10^{-2}$	$8.3\ 10^{-2}$	$2.7\ 10^{-1}$	$2.6\ 10^{-1}$	$9.2\ 10^{-1}$	$2.9\ 10^{-5}$	$1.2\ 10^{-5}$	$3.8\ 10^{-6}$	$5.0\ 10^{-6}$	$1.5\ 10^{-6}$	$6.1\ 10^{-7}$
Grafenrheinfeld	$2.7\ 10^{-1}$	$3.6\ 10^{-1}$	$3.2\ 10^{-1}$	$5.0\ 10^{-2}$	$5.8\ 10^{-2}$	$5.0\ 10^{-2}$	$1.5\ 10^{-6}$	$1.8\ 10^{-6}$	$1.9\ 10^{-6}$	–	–	–
Grohnde/ Emmerthal	$2.6\ 10^{-1}$	$5.2\ 10^{-1}$	$3.8\ 10^{-1}$	$3.3\ 10^{-1}$	$4.0\ 10^{-1}$	$2.6\ 10^{-1}$	–	–	–	–	–	–
Isar 1	$8.1\ 10^{-2}$	$9.3\ 10^{-2}$	$9.1\ 10^{-2}$	$2.9\ 10^{-1}$	$3.4\ 10^{-1}$	$2.4\ 10^{-1}$	$2.2\ 10^{-6}$	$3.9\ 10^{-6}$	–	–	–	–
Isar 2	$4.8\ 10^{-1}$	$5.9\ 10^{-1}$	$3.0\ 10^{-1}$	$5.4\ 10^{-1}$	$5.8\ 10^{-1}$	$1.2\ 10^{-1}$	–	–	–	–	–	–
Krümmel/ Geesthacht	$3.9\ 10^{-2}$	$3.5\ 10^{-2}$	$4.1\ 10^{-2}$	$4.8\ 10^{-1}$	$3.6\ 10^{-1}$	$2.5\ 10^{-1}$	$5.7\ 10^{-6}$	$3.6\ 10^{-6}$	$7.4\ 10^{-6}$	–	–	$5.2\ 10^{-8}$
Lingen/Emsland	$2.5\ 10^{0}$	$1.6\ 10^{0}$	$1.5\ 10^{0}$	$7.0\ 10^{-1}$	$3.2\ 10^{-1}$	$3.6\ 10^{-1}$	–	$1.1\ 10^{-7}$	$1.2\ 10^{-7}$	–	–	–
Lingen	$2.6\ 10^{-4}$	$1.9\ 10^{-4}$	$1.3\ 10^{-4}$	$7.8\ 10^{-4}$	$6.8\ 10^{-4}$	$3.9\ 10^{-4}$	$8.2\ 10^{-9}$	$6.9\ 10^{-1}1$	$8.4\ 10^{-1}0$	$3.6\ 10^{-8}$	$4.9\ 10^{-9}$	$2.7\ 10^{-9}$
Mülheim-Kärlich	$2.9\ 10^{-2}$	$1.7\ 10^{-2}$	$1.9\ 10^{-3}$	$5.1\ 10^{-4}$	–	–	–	–	–	–	–	–
Neckar-westheim 1	$1.3\ 10^{-1}$	$1.1\ 10^{-1}$	$1.2\ 10^{-1}$	$2.4\ 10^{-1}$	$2.4\ 10^{-1}$	$1.7\ 10^{-1}$	$7.4\ 10^{-8}$	$4.3\ 10^{-7}$	$7.3\ 10^{-7}$	–	–	–
Neckar-westheim 2	$2.6\ 10^{-1}$	$2.5\ 10^{-1}$	$1.4\ 10^{-1}$	$2.7\ 10^{-1}$	$3.9\ 10^{-1}$	$2.6\ 10^{-1}$	–	$1.9\ 10^{-6}$	–	–	$1.8\ 10^{-7}$	–
Obrigheim	$1.3\ 10^{-1}$	$1.3\ 10^{-1}$	$9.8\ 10^{-2}$	$4.7\ 10^{-2}$	$8.4\ 10^{-2}$	$5.6\ 10^{-2}$	$7.6\ 10^{-7}$	$6.5\ 10^{-7}$	$2.2\ 10^{-6}$	$1.5\ 10^{-7}$	$2.8\ 10^{-8}$	$1.5\ 10^{-8}$
Philippsburg KKP1	$5.5\ 10^{-2}$	$5.2\ 10^{-2}$	$4.8\ 10^{-2}$	$6.2\ 10^{-1}$	$5.0\ 10^{-1}$	$5.3\ 10^{-1}$	$4.5\ 10^{-6}$	$4.6\ 10^{-6}$	$3.4\ 10^{-6}$	$4.0\ 10^{-7}$	$2.0\ 10^{-7}$	$3.7\ 10^{-7}$
Philippsburg KKP2	$1.1\ 10^{0}$	$5.4\ 10^{-1}$	$3.0\ 10^{-1}$	$1.8\ 10^{-1}$	$1.9\ 10^{-1}$	$2.9\ 10^{-1}$	$1.2\ 10^{-7}$	$1.9\ 10^{-7}$	$1.4\ 10^{-7}$	$6.5\ 10^{-8}$	$3.8\ 10^{-8}$	$3.8\ 10^{-8}$
Rheinsberg	–	–	–	–	–	–	$2.9\ 10^{-7}$	$2.8\ 10^{-7}$	$2.1\ 10^{-7}$	$2.0\ 10^{-7}$	$3.8\ 10^{-7}$	$2.0\ 10^{-7}$
Stade	$5.3\ 10^{-1}$	$5.5\ 10^{-1}$	$7.3\ 10^{-1}$	$1.9\ 10^{-1}$	$9.1\ 10^{-2}$	$1.5\ 10^{-1}$	$4.0\ 10^{-7}$	$1.4\ 10^{-6}$	$1.0\ 10^{-6}$	$1.4\ 10^{-7}$	$8.3\ 10^{-7}$	$9.2\ 10^{-8}$
Rodenkirchen-Unterweser	$4.4\ 10^{-1}$	$3.3\ 10^{-1}$	$3.1\ 10^{-1}$	$3.7\ 10^{-2}$	$5.6\ 10^{-2}$	$6.0\ 10^{-2}$	$1.5\ 10^{-6}$	$4.5\ 10^{-7}$	$6.9\ 10^{-7}$	–	–	–
Würgassen/ Beverungen	$3.6\ 10^{-3}$	$3.0\ 10^{-3}$	$1.4\ 10^{-2}$	$2.7\ 10^{-4}$	$1.3\ 10^{-3}$	$1.4\ 10^{-3}$	$7.0\ 10^{-6}$	$4.8\ 10^{-6}$	$3.0\ 10^{-6}$	$1.1\ 10^{-5}$	$2.5\ 10^{-6}$	$1.8\ 10^{-6}$
Switzerland												
Beznau	–	–	–	$4.0\ 10^{-2}$	$4.0\ 10^{-2}$	$4.0\ 10^{-2}$	–	–	–	–	–	–
Gösgen	–	–	–	$1.0\ 10^{-1}$	$1.0\ 10^{-1}$	$4.0\ 10^{-1}$	–	–	–	–	–	–
Leibstadt	$4.7\ 10^{-1}$	$1.3\ 10^{0}$	$8.2\ 10^{-1}$	$6.5\ 10^{-1}$	$5.1\ 10^{-1}$	$4.5\ 10^{-1}$	–	–	–	–	–	–
Mühleberg	–	–	–	$2.0\ 10^{-1}$	$2.0\ 10^{-1}$	$2.0\ 10^{-1}$	–	–	–	–	–	–

Liquid discharges

Reactor	Liquid discharges (TBq)								
	Tritium			Cobalt-60			Caesium-137		
	1999	2000	2001	1999	2000	2001	1999	2000	2001
United Kingdom									
Berkeley	$6.4\ 10^{-3}$	$6.4\ 10^{-3}$	$7.4\ 10^{-4}$	$6.8\ 10^{-5}$	$6.4\ 10^{-5}$	$3.6\ 10^{-5}$	$7.7\ 10^{-3}$	$1.7\ 10^{-2}$	$2.3\ 10^{-3}$
Bradwell	$5.2\ 10^{-1}$	$6.5\ 10^{-1}$	$1.8\ 10^{0}$	$1.1\ 10^{-3}$	$3.5\ 10^{-4}$	$4.0\ 10^{-4}$	$3.4\ 10^{-1}$	$4.9\ 10^{-1}$	$4.7\ 10^{-1}$
Chapelcross	$7.1\ 10^{-1}$	$5.5\ 10^{-1}$	$1.7\ 10^{-1}$	$4.0\ 10^{-4}$	$7.0\ 10^{-4}$	$3.0\ 10^{-1}$	$3.8\ 10^{-3}$	$1.7\ 10^{-2}$	$4.2\ 10^{-3}$
Dungeness A	$2.1\ 10^{0}$	$1.1\ 10^{0}$	$2.4\ 10^{0}$	$3.3\ 10^{-4}$	$2.5\ 10^{-4}$	–	$3.3\ 10^{-1}$	$1.3\ 10^{-1}$	$1.1\ 10^{-1}$
Dungeness B	$1.2\ 10^{2}$	$1.2\ 10^{2}$	$3.6\ 10^{2}$	$2.0\ 10^{-3}$	$1.5\ 10^{-3}$	$2.4\ 10^{-3}$	–	–	–
Hartlepool	$4.1\ 10^{2}$	$4.1\ 10^{2}$	$3.9\ 10^{2}$	$3.1\ 10^{-3}$	$3.3\ 10^{-3}$	$2.0\ 10^{-3}$	–	–	–
Heysham 1	$4.0\ 10^{2}$	$4.4\ 10^{2}$	$4.0\ 10^{2}$	$3.0\ 10^{-4}$	$1.1\ 10^{-3}$	$7.9\ 10^{-4}$	–	–	–
Heysham 2	$2.6\ 10^{2}$	$3.4\ 10^{2}$	$3.3\ 10^{2}$	$1.0\ 10^{-3}$	$3.7\ 10^{-4}$	$2.3\ 10^{-4}$	–	–	–
Hinkley Point A	$1.0\ 10^{0}$	$1.3\ 10^{0}$	$1.1\ 10^{0}$	$1.5\ 10^{-3}$	$8.1\ 10^{-4}$	$8.6\ 10^{-4}$	$4.4\ 10^{-1}$	$3.0\ 10^{-1}$	$4.3\ 10^{-1}$
Hinkley Point B	$3.6\ 10^{2}$	$3.5\ 10^{2}$	$4.2\ 10^{2}$	$4.2\ 10^{-4}$	$3.0\ 10^{-4}$	$4.5\ 10^{-4}$	–	–	–
Hunterston A	$2.2\ 10^{-2}$	$2.8\ 10^{-3}$	$4.0\ 10^{-3}$	–	–	–	$1.7\ 10^{-1}$	$1.2\ 10^{-1}$	$1.3\ 10^{-1}$
Hunterston B	$4.2\ 10^{2}$	$3.3\ 10^{2}$	$4.8\ 10^{2}$	$9.9\ 10^{-4}$	$4.7\ 10^{-4}$	$4.1\ 10^{-4}$			
Oldbury	$2.1\ 10^{-1}$	$3.5\ 10^{-1}$	$3.4\ 10^{-1}$	$2.1\ 10^{-4}$	$2.1\ 10^{-4}$	$1.9\ 10^{-4}$	$6.6\ 10^{-2}$	$6.4\ 10^{-2}$	$4.8\ 10^{-1}$
Sizewell A	$6.6\ 10^{-1}$	$1.6\ 10^{0}$	$2.0\ 10^{0}$	$1.2\ 10^{-4}$	$1.0\ 10^{-4}$	$5.2\ 10^{-4}$	$6.9\ 10^{-2}$	$1.4\ 10^{-1}$	$7.6\ 10^{-1}$
Sizewell B	$5.6\ 10^{1}$	$5.3\ 10^{1}$	$6.4\ 10^{1}$	–	–	–	–	–	–
Torness	$3.3\ 10^{2}$	$2.3\ 10^{2}$	$2.7\ 10^{2}$	$4.2\ 10^{-4}$	$3.5\ 10^{-4}$	$1.5\ 10^{-4}$	–	–	–
Trawsfynydd	$3.8\ 10^{-2}$	$5.3\ 10^{-3}$	$2.9\ 10^{-2}$	$1.3\ 10^{-4}$	–	–	$3.7\ 10^{-3}$	$1.8\ 10^{-3}$	$1.9\ 10^{-3}$
Wylfa	$4.6\ 10^{0}$	$4.0\ 10^{0}$	$6.4\ 10^{0}$	$1.3\ 10^{-3}$	$1.4\ 10^{-3}$	$1.5\ 10^{-3}$	$1.3\ 10^{-3}$	$1.0\ 10^{-2}$	$1.8\ 10^{-2}$
France									
Belleville	$3.2\ 10^{1}$	$3.9\ 10^{1}$	$4.9\ 10^{1}$	$1.7\ 10^{-3}$	$6.3\ 10^{-4}$	$3.5\ 10^{-4}$	$8.5\ 10^{-5}$	$6.5\ 10^{-5}$	$5.9\ 10^{-5}$
Bugey	$3.4\ 10^{1}$	$3.5\ 10^{1}$	$2.8\ 10^{1}$	$9.4\ 10^{-4}$	$8.5\ 10^{-4}$	$3.9\ 10^{-4}$	$4.3\ 10^{-4}$	$1.4\ 10^{-4}$	$1.1\ 10^{-4}$
Cattenom	$8.7\ 10^{1}$	$8.6\ 10^{1}$	$1.1\ 10^{2}$	$4.3\ 10^{-4}$	$3.6\ 10^{-4}$	$1.7\ 10^{-4}$	$2.7\ 10^{-4}$	$8.3\ 10^{-5}$	$7.2\ 10^{-5}$
Chinon	$4.1\ 10^{1}$	$3.8\ 10^{1}$	$3.9\ 10^{1}$	$4.3\ 10^{-4}$	$1.1\ 10^{-4}$	$1.4\ 10^{-4}$	$7.8\ 10^{-5}$	$7.8\ 10^{-5}$	$7.3\ 10^{-5}$
Chooz	$2.0\ 10^{1}$	$3.7\ 10^{1}$	$3.9\ 10^{1}$	$1.4\ 10^{-4}$	$1.5\ 10^{-4}$	$4.0\ 10^{-5}$	$1.5\ 10^{-4}$	$2.8\ 10^{-5}$	$1.5\ 10^{-5}$
Civaux	$3.6\ 10^{0}$	$2.6\ 10^{1}$	$1.6\ 10^{1}$	$5.4\ 10^{-5}$	$2.4\ 10^{-5}$	$2.4\ 10^{-5}$	$1.1\ 10^{-5}$	$2.3\ 10^{-5}$	$1.4\ 10^{-5}$
Cruas	$4.4\ 10^{1}$	$4.6\ 10^{1}$	$4.0\ 10^{1}$	$3.0\ 10^{-4}$	$4.2\ 10^{-4}$	$1.4\ 10^{-4}$	$8.2\ 10^{-5}$	$4.8\ 10^{-5}$	$3.6\ 10^{-5}$
Dampierre en-Burly	$4.0\ 10^{1}$	$3.2\ 10^{1}$	$3.5\ 10^{1}$	$1.6\ 10^{-5}$	$7.1\ 10^{-4}$	$6.8\ 10^{-4}$	$3.3\ 10^{-4}$	$1.2\ 10^{-4}$	$2.2\ 10^{-4}$
Fessenheim	$2.1\ 10^{1}$	$1.8\ 10^{1}$	$2.3\ 10^{1}$	$1.2\ 10^{-3}$	$1.9\ 10^{-4}$	$7.6\ 10^{-5}$	$4.0\ 10^{-5}$	$5.2\ 10^{-5}$	$5.4\ 10^{-5}$
Flamanville	$2.5\ 10^{1}$	$4.7\ 10^{1}$	$5.8\ 10^{1}$	$1.3\ 10^{-4}$	$8.2\ 10^{-4}$	$3.9\ 10^{-4}$	$8.1\ 10^{-4}$	$2.3\ 10^{-4}$	$2.6\ 10^{-5}$
Golfech	$2.3\ 10^{1}$	$2.7\ 10^{1}$	$4.9\ 10^{1}$	$5.8\ 10^{-4}$	$2.1\ 10^{-4}$	$1.4\ 10^{-4}$	$3.1\ 10^{-4}$	$8.5\ 10^{-5}$	$9.7\ 10^{-5}$
Gravelines	$4.6\ 10^{1}$	$4.7\ 10^{1}$	$5.3\ 10^{1}$	$6.4\ 10^{-4}$	$6.6\ 10^{-4}$	$8.9\ 10^{-4}$	$1.7\ 10^{-4}$	$9.7\ 10^{-5}$	$9.1\ 10^{-5}$
Le Blayais	$6.8\ 10^{1}$	$3.6\ 10^{1}$	$4.7\ 10^{1}$	$1.1\ 10^{-3}$	$7.6\ 10^{-4}$	$1.7\ 10^{-4}$	$9.2\ 10^{-5}$	$1.4\ 10^{-4}$	$2.7\ 10^{-5}$
Nogent-sur-Seine	$5.0\ 10^{1}$	$6.2\ 10^{1}$	$5.3\ 10^{1}$	$6.2\ 10^{-4}$	$6.0\ 10^{-4}$	$7.2\ 10^{-4}$	$6.4\ 10^{-5}$	$5.2\ 10^{-5}$	$9.2\ 10^{-5}$
Paluel	$8.4\ 10^{1}$	$1.1\ 10^{2}$	$1.0\ 10^{2}$	$1.8\ 10^{-3}$	$7.8\ 10^{-4}$	$1.8\ 10^{-3}$	$5.0\ 10^{-4}$	$4.0\ 10^{-4}$	$3.4\ 10^{-4}$
Penly	$3.3\ 10^{1}$	$3.5\ 10^{1}$	$4.5\ 10^{1}$	$2.1\ 10^{-4}$	$3.2\ 10^{-4}$	$2.7\ 10^{-4}$	$4.2\ 10^{-4}$	$1.6\ 10^{-4}$	$1.8\ 10^{-4}$
Saint Laurent	$2.4\ 10^{1}$	$2.4\ 10^{1}$	$2.6\ 10^{1}$	$3.1\ 10^{-4}$	$3.6\ 10^{-4}$	$2.8\ 10^{-4}$	$6.6\ 10^{-5}$	$8.6\ 10^{-5}$	$3.9\ 10^{-5}$
Tricastin	$2.9\ 10^{1}$	$4.0\ 10^{1}$	$4.3\ 10^{1}$	$7.7\ 10^{-4}$	$5.3\ 10^{-4}$	$2.8\ 10^{-4}$	$2.3\ 10^{-4}$	$2.7\ 10^{-4}$	$3.4\ 10^{-5}$

Reactor	Liquid discharges (TBq)								
	Tritium			Cobalt-60			Caesium-137		
	1999	2000	2001	1999	2000	2001	1999	2000	2001
Germany									
Biblis A	$1.6\ 10^{1}$	$1.6\ 10^{1}$	$7.7\ 10^{0}$	$2.3\ 10^{-5}$	$5.8\ 10^{-5}$	$3.7\ 10^{-5}$	$2.9\ 10^{-6}$	$5.9\ 10^{-6}$	$1.2\ 10^{-6}$
Biblis B	$1.6\ 10^{1}$	$1.5\ 10^{1}$	$1.1\ 10^{1}$	$2.7\ 10^{-5}$	$1.5\ 10^{-5}$	$1.4\ 10^{-4}$	$2.3\ 10^{-5}$	$2.3\ 10^{-6}$	$1.2\ 10^{-5}$
Brokdorf	$1.8\ 10^{1}$	$2.1\ 10^{1}$	$2.0\ 10^{1}$	$7.7\ 10^{-7}$	$2.1\ 10^{-6}$	$6.5\ 10^{-7}$	$3.1\ 10^{-6}$	$1.2\ 10^{-6}$	$6.8\ 10^{-6}$
Brunsbüttel	$2.6\ 10^{-1}$	$3.5\ 10^{-1}$	$3.1\ 10^{-1}$	$1.6\ 10^{-4}$	$7.8\ 10^{-5}$	$7.9\ 10^{-5}$	$3.5\ 10^{-5}$	$3.0\ 10^{-5}$	$2.5\ 10^{-5}$
Grafenrheinfeld	$1.4\ 10^{1}$	$1.6\ 10^{1}$	$1.6\ 10^{1}$	$1.9\ 10^{-5}$	$3.1\ 10^{-5}$	$1.7\ 10^{-5}$	–	$9.0\ 10^{-7}$	$8.3\ 10^{-8}$
Grohnde/Emmerthal	$1.9\ 10^{1}$	$1.7\ 10^{1}$	$1.3\ 10^{1}$	$3.8\ 10^{-6}$	$8.9\ 10^{-6}$	$2.8\ 10^{-6}$	–	$9.4\ 10^{-8}$	$1.3\ 10^{-7}$
Isar 1	$3.5\ 10^{-1}$	$4.3\ 10^{-1}$	$8.4\ 10^{-1}$	$4.4\ 10^{-5}$	$3.5\ 10^{-5}$	$7.0\ 10^{-5}$	$6.6\ 10^{-6}$	$7.1\ 10^{-6}$	$1.8\ 10^{-5}$
Isar 2	$2.4\ 10^{1}$	$1.8\ 10^{1}$	$2.0\ 10^{1}$	–	$2.3\ 10^{-6}$	–	–	$2.0\ 10^{-6}$	–
Kahl	$3.3\ 10^{-5}$	$1.6\ 10^{-3}$	$2.9\ 10^{-4}$	$6.5\ 10^{-6}$	$8.5\ 10^{-6}$	$6.2\ 10^{-6}$	$3.1\ 10^{-6}$	$2.8\ 10^{-6}$	$2.8\ 10^{-6}$
Krümmel/Geesthacht	$3.5\ 10^{-1}$	$5.0\ 10^{-1}$	$4.3\ 10^{1}$	$1.9\ 10^{-6}$	$9.8\ 10^{-7}$	$9.3\ 10^{-6}$	–	–	–
Lingen/Emsland	$1.7\ 10^{-1}$	$1.3\ 10^{1}$	$1.8\ 10^{1}$	–	–	$2.6\ 10^{-8}$	–	–	–
Lingen	–	$7.1\ 10^{-6}$	$2.4\ 10^{-4}$	–	$1.6\ 10^{-7}$	$1.4\ 10^{-6}$	–	$1.4\ 10^{-7}$	$1.6\ 10^{-6}$
Mülheim-Kärlich	$9.0\ 10^{-3}$	$1.1\ 10^{-1}$	$5.3\ 10^{-3}$	$6.4\ 10^{-6}$	$8.1\ 10^{-6}$	$8.3\ 10^{-6}$	–	–	–
Neckar-westheim 1	$6.7\ 10^{0}$	$8.7\ 10^{0}$	$9.5\ 10^{0}$	$5.0\ 10^{-7}$	$6.5\ 10^{-8}$	$5.1\ 10^{-7}$	–	–	–
Neckar-westheim 2	$1.7\ 10^{1}$	$1.1\ 10^{1}$	$9.5\ 10^{0}$	$2.5\ 10^{-6}$	$1.9\ 10^{-6}$	$1.9\ 10^{-7}$	$1.4\ 10^{-5}$	$1.8\ 10^{-7}$	$1.1\ 10^{-7}$
Obrigheim	$6.1\ 10^{0}$	$5.5\ 10^{0}$	$5.4\ 10^{0}$	$1.1\ 10^{-4}$	$1.8\ 10^{-4}$	$2.8\ 10^{-5}$	$1.1\ 10^{-5}$	$6.6\ 10^{-5}$	$7.7\ 10^{-6}$
Philippsburg KKP1	$5.9\ 10^{-1}$	$4.8\ 10^{-1}$	$6.5\ 10^{-1}$	$9.5\ 10^{-5}$	$7.7\ 10^{-5}$	$6.3\ 10^{-5}$	$1.8\ 10^{-5}$	$4.7\ 10^{-6}$	$7.9\ 10^{-6}$
Philippsburg KKP2	$1.8\ 10^{1}$	$1.8\ 10^{1}$	$1.3\ 10^{1}$	$3.7\ 10^{-5}$	$5.0\ 10^{-5}$	$8.1\ 10^{-5}$	$1.5\ 10^{-4}$	$1.3\ 10^{-4}$	$1.6\ 10^{-4}$
Rheinsberg	–	–	–	$2.4\ 10^{-6}$	$1.7\ 10^{-6}$	$1.0\ 10^{-6}$	$1.9\ 10^{-6}$	$2.1\ 10^{-6}$	$1.0\ 10^{-6}$
Stade	$3.0\ 10^{0}$	$2.4\ 10^{0}$	$5.1\ 10^{0}$	$1.1\ 10^{-5}$	$9.3\ 10^{-6}$	$3.7\ 10^{-5}$	$6.8\ 10^{-6}$	$5.5\ 10^{-6}$	$6.5\ 10^{-6}$
Rodenkirchen-Unterweser	$7.7\ 10^{0}$	$1.6\ 10^{1}$	$1.6\ 10^{1}$	$2.5\ 10^{-5}$	$1.4\ 10^{-4}$	$2.9\ 10^{-5}$	$1.4\ 10^{-6}$	$8.8\ 10^{-5}$	$1.2\ 10^{-5}$
Würgassen/Beverungen	$1.6\ 10^{-2}$	$8.0\ 10^{-4}$	$8.0\ 10^{-4}$	$6.3\ 10^{-5}$	$2.6\ 10^{-5}$	$1.4\ 10^{-6}$	$3.7\ 10^{-5}$	$1.7\ 10^{-5}$	$1.5\ 10^{-5}$
Switzerland									
Beznau	$8.8\ 10^{0}$	$8.3\ 10^{0}$	$1.1\ 10^{1}$	$1.7\ 10^{-3}$	$3.1\ 10^{-3}$	$1.6\ 10^{-3}$	$1.3\ 10^{-3}$	$1.7\ 10^{-3}$	$8.7\ 10^{-4}$
Gösgen	$1.4\ 10^{1}$	$1.4\ 10^{1}$	$1.2\ 10^{1}$	$1.1\ 10^{-6}$	$2.6\ 10^{-6}$	$1.1\ 10^{-6}$	–	–	$8.2\ 10^{-8}$
Leibstadt	$7.0\ 10^{-1}$	$1.7\ 10^{0}$	$1.1\ 10^{0}$	$5.0\ 10^{-5}$	$1.3\ 10^{-4}$	$1.3\ 10^{-4}$	$2.3\ 10^{-5}$	$5.3\ 10^{-5}$	$4.0\ 10^{-5}$
Mühleberg	$1.7\ 10^{-1}$	$1.4\ 10^{-1}$	$2.0\ 10^{-1}$	$1.8\ 10^{-3}$	$1.7\ 10^{-3}$	$5.1\ 10^{-3}$	$1.1\ 10^{-2}$	$3.3\ 10^{-3}$	$3.2\ 10^{-3}$

APPENDIX E

REPORTS OF THE COMMITTEE ON MEDICAL ASPECTS OF RADIATION IN THE ENVIRONMENT

COMARE Thirteenth Report. The health effects and risks arising from exposure to ultraviolet radiation from artificial tanning devices. HPA, Chilton, June 2009.

COMARE Twelfth Report. The impact of personally initiated X-ray computed tomography scanning for the health assessment of asymptomatic individuals. HPA, Chilton, December 2007.

COMARE Eleventh Report. The distribution of childhood leukaemia and other childhood cancer in Great Britain 1969-1993. HPA, Chilton, July 2006.

COMARE Tenth Report. The incidence of childhood cancer around nuclear installations in Great Britain. HPA, Chilton, June 2005.

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APPENDIX F

COMMITTEE ON MEDICAL ASPECTS OF RADIATION IN THE ENVIRONMENT

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Dr K Broom BSc DPhil CBiol FSB (Scientific)

Ms K Stonell (Minutes)

Ms J Humphries (Administrative)

ASSESSORS IN ATTENDANCE REPRESENTING THE FOLLOWING ORGANISATIONS

Department for Children, Schools and Families

Department for Communities and Local Government

Department of Energy and Climate Change

Department of the Environment, Food and Rural Affairs

Department of Health

Department of Health, Social Services and Public Safety (Northern Ireland)
Department for Innovation, Universities and Skills
Environment Agency
Food Standards Agency
Health Protection Agency
Health and Safety Executive
Information Services Division, NHS Scotland
Medical Research Council
Ministry of Defence
Nuclear Decommissioning Authority
Office for National Statistics
Scottish Environment Protection Agency
Scottish Government
Welsh Assembly Government

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APPENDIX G

DECLARATION OF MEMBERS' INTERESTS CODE OF PRACTICE

1 Introduction

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.

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 radiation industry generally and, less frequently, to commercial interests involving radioactivity. It is therefore essential that members should comply with the code of practice which is set out below.

2 Scope and definitions

This code applies to members of COMARE and its subcommittees, subgroups, working groups and working parties which may be formed.

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 and also medical service industries;

(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.

This excludes government departments, professional bodies, international organisations and agencies.

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.

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

3 Different types of interest – definitions

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 they 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. Members of the Committee and the Secretariat are under no 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.

3.1 *Personal interests*

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

(a) *Consultancies and/or direct 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.

(d) *Membership or affiliation:* any membership role or affiliation that the member or close family member has to clubs or organisations with an interest or involvement in the work of the Department. This will not include professional bodies, organisations and societies.

3.2 *Non-personal interests*

A non-personal interest involves current payment which benefits a department to 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 a unit or department 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 or department for which a 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.

(d) *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.

3.3 *Specific interests*

A specific interest relates explicitly to the material, product, substance or application under consideration by the Committee.

A member must declare a personal, specific interest if they currently receive a payment, in any form, for any significant fundamental development work undertaken previously or at this time, on a material, product or substance or its application under consideration. This will include the production of radioactive substances and devices designed to use ionising or non-ionising radiation for diagnostic, treatment or other purposes.

A member must declare a non-personal, specific interest if they are aware that the department to which they are responsible currently receives payment for significant fundamental development work undertaken previously or at this time, on a material, product or substance or its application under consideration but they have not personally received payment for that work in any form. This will include the production of radioactive substances and devices designed to use ionising or non-ionising radiation for diagnostic, treatment or other purposes.

3.4 *Non-specific interests*

A non-specific interest relates to a company or associated material, product, substance or application, but not to the specific material, product, substance or application under consideration by the Committee.

A member must declare a personal, non-specific interest if they have a current personal interest with a material, product, substance or application from a particular company, which does not relate specifically to the material, product, substance or application from that company under consideration.

A member must declare a non-personal, non-specific interest if they are aware that the department to which they are responsible is currently receiving payment from the company concerned which does not relate specifically to a material, product, substance or application under discussion.

If a member is aware that a material, product, substance or their application under consideration is or may become a competitor of a material, product or substance manufactured, sold or supplied by a company in which the member has a current personal interest, they should declare their interest in the company marketing the rival material, product or substance.

Members are under no obligation to seek out knowledge of such work done for or on behalf of the radiation industry within departments to which they are responsible if they would not reasonably expect to be informed. This applies to all non-personal, specific and non-specific interests.

4 Declaration of interests

4.1 *Declaration of interests to the Secretariat*

Members should inform the Secretariat 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. An interest is *current* if the member has a continuing financial involvement with the industry, eg if they hold shares in a radiation company, have a consultancy contract, or if the member or the department to which they are responsible is in the process of carrying out work for the radiation industry. Members are asked to inform the Secretariat at the time of any change in their personal interests, and may be invited to complete a form of declaration when required. 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 £5000 from a particular company in the previous year need not be declared.)

The register of interests should be kept up-to-date and be open to the public.

4.2 *Declaration of interests at meetings and participation by members*

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, they 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.

A member, who is in any doubt as to whether they have 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.

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, they 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.

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

4.3 *Members' declarations of interests – 2010*

Member	Company	Personal interest	Company	Non-personal interest
Dr J Bithell		None		None
Prof A Elliott		None		None
Dr W Evans		None		None
Prof T Helleday		None	MRC	Support for research
Prof S V Hodgson		None	CR-UK	Support for research
Prof P Hoskin		None		None
Dr B Howard		None		None
Prof P Jeggo		None		None
Dr P Marsden		None		None
Dr G Maskell		None		None
Dr C D Mitchell		None		None
Dr M Murphy		None		None
Dr M Pearce		None		None
Dr J Verne		None		None
Prof R Wakeford	1 Sellafield Ltd	Consultancy		None
	2 Compensation Scheme for Radiation-linked Diseases	Consultancy		
	3 Canadian Nuclear Safety Commission	Contract		
	4 Augean	Contract		
Prof P Warwick	Enviras Ltd	Director and shareholder	NDA	Grants