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Ionising Radiation and Childhood Leukaemia

(Revision of SSK Volume 29)

Statement by the German Commission on Radiological Protection

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Statement by the German Commission on Radiological Protection

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Preface

In 1994 the Commission on Radiological Protection (SSK) issued an statement entitled "Ionising Radiation and Childhood Leukaemia", which was published in SSK volume 29.

In 2007 the Federal Ministry for the Environment, Nature Conservation and Nuclear Safety assigned the Commission the task of evaluating newly published scientific findings and producing a revised statement based on this evaluation.

The SSK working group established to draw up this document consists of the following members:

- Prof. Dr. Joachim Breckow, Technische Hochschule Mittelhessen (THM), physicist
- Prof. Dr. Wolfgang Dörr, Technische Universität Dresden, radiobiologist
- Dipl.-Phys. Franz Fehringer, Berufsgenossenschaft Elektro Textil Feinmechanik (BGETF), physicist
- PD Dr. Anna Friedl, Universität München, radiobiologist
- Prof. Dr. Wolfgang-Ulrich Müller, Universität Essen, radiobiologist (chair)
- PD Dr. Claudia Spix, Deutsches Kinderkrebsregister (DKKR) Mainz, epidemiologist
- Prof. Dr. Brigitte Stöver, Charité Berlin, children's radiologist
- Prof. Dr. Dr. Heinz-Erich Wichmann, Helmholtz-Zentrum München, epidemiologist.

In 2008, the work of the group was interrupted for over a year to allow for the completion of the statement and scientific reasoning of the "Assessment of the Epidemiological Study on Childhood Cancer in the Vicinity of Nuclear Power Plants" (KiKK Study), which was published in issues 57 and 58 in the series "SSK Reports". Further to these two SSK publications, this volume gives a comprehensive overview of this complex interdisciplinary field of research. In this volume the current findings are presented from the areas of medicine, radiobiology, molecular biology, immunology, epidemiology and statistics relating to the development of leukaemia in children and adolescents.

This volume was completed on 11 February 2011, prior to the publication of the COMARE 11 Report and the Swiss CANUPIS Study, thus they could not be taken account of in this statement.

To the Commission on Radiological Protection it is a great concern to contribute to a better understanding of the causes of leukaemia in childhood and adolescence.

Bonn, November 2011

Prof. R. Michel	*Prof. W.-U. Müller*
SSK Chair	Working Group Chair

Content

Ionising Radiation and Childhood Leukaemia (Revision of SSK Volume 29)

Statement by the German Commission on Radiological Protection

Adopted at the 250th meeting of the German Commission on Radiological Protection on 29/30 September 2011

Publication of the Commission on Radiological Protection • Volume 69 A

Content

1 Introduction

Various studies have found a correlation between the risk of developing childhood leukaemia and the proximity of the home to the nearest nuclear power plant (NPP). However, radiation dose estimates and measurements carried out in the vicinity of these plants show that the doses are so low, by orders of magnitude, that they cannot explain the increased incidence of leukaemia observed in some studies. In addition, at least some of the studies found increased frequencies of childhood leukaemia in the vicinity of planned sites of nuclear power plants and pre-operational nuclear power plant sites, suggesting that factors other than exposure to ionising radiation are significant in these cases.

The greatest difficulty arising at present when interpreting the available data is that the mechanisms of leukaemia induction and development in children are unknown. However, it seems likely that as with solid cancers, the development of leukaemias is a multistep process, and that the various steps are not necessarily caused by the same agent. It is therefore highly probable that leukaemia development is a multifactorial process. This makes it more difficult to conduct epidemiological studies, as the contributions of the various individual factors may be small and all the relevant factors may have to interact in order to cause leukaemia. There are strong indications that the first step, at least, may be established during pregnancy, especially in children younger than five.

The present volume, which replaces SSK Volume 29 (SSK 1994), reviews the current scientific knowledge about the development of childhood leukaemias, both in general terms and in relation to ionising radiation in particular, in the fields of molecular biology, immunology and epidemiology, and considers various risk factors. The reason why this paper considers not only ionising radiation but other factors as well reflects the fact that as described above, the development of childhood leukaemias is presumably a multifactorial process. The many gaps in our scientific understanding of how leukaemias develop in childhood can only be identified by adopting a comprehensive approach to this issue.

2 Childhood leukaemia: medical aspects

Leukaemia is a malignant neoplasm of stem cells in the blood-forming or lymphatic system, characterised by increased numbers of leukocytes and their precursors in both the bone marrow and peripheral blood.

The classification systems for leukaemia are constantly developing. Classification is based on morphological and immunological features. The disease is generally classified as acute lymphoblastic leukaemia (ALL) when there are > 25 % malignant lymphoblasts in the bone marrow. The presence of > 25 % myeloblasts in blood (nor-

mal level: < 20 %) is defined as the typical pathology of acute myeloid leukaemia (AML). Chronic myeloid leukaemia (CML) is extremely rare in children and will not be considered further here. Children almost never contract chronic lymphocytic leukaemia (CLL) and in adults it is caused, if at all, by exposure to high doses of radiation only. For that reason, it will also not be considered in more detail here.

The prognoses for children with cancers, especially leukaemias and related diseases, have improved dramatically in recent years. For ALL, a risk-adapted polychemotherapy regime is associated with a favourable prognosis of disease-free survival of 60-90 %[a]. A rate of complete remission of 60-80% and a good prognosis can also be achieved for AML, although disease-free survival with no relapse is as low as 20-30 %.

3 Descriptive epidemiology

Childhood cancer, leukaemias and related diseases are rare in children and juveniles. In Germany, an average of 1 820 new cases of cancer in the under-15s were diagnosed each year during the period 1999-2008, with leukaemias and related diseases accounting for 620 of these cases on average. The incidence rate for malignant tumours was 160 cases per million children (aged 0 to no older than 15) per year, with ALL accounting for 44 cases per million children per year (27 %) and AML accounting for 7.4 cases per million children per year (4.6 %). The incidence rate for all childhood leukaemias in Germany for the period 1999-2008 was 55 cases per million children per year. The mean cumulative risk for the under-15s is $7.9 \cdot 10^{-4}$. In other words, for every 1 270 newborns, one case of childhood leukaemia is diagnosed before they reach 15 years of age. The median age at diagnosis is 4.8 years for ALL and 5.8 years for AML. Certain conditions, notably Down's syndrome , are associated with an increased leukaemia risk.

One problem affecting statistical analysis is that the terminology relating to childhood leukaemias is not fully standardised in the international epidemiological literature. It is only possible to determine precisely what is meant if the underlying classification system is specified, but this is not always the case. Relevant classification systems are the International Classification of Diseases (ICD), the International Classification of Diseases for Oncology (ICD-O) and, in particular, the International Classification of Childhood Cancer (ICCC). The ICD and ICD-O classification systems are published by the World Health Organization (WHO). Country-specific versions of these two systems also exist. The ICCC was developed by a working group set up by the International Agency for Research on Cancer (IARC).

[a] Originally, the review period was just five years. As the results of long-term monitoring are now available, this timespan has been extended to 15 years and more.

Epidemiological statements about leukaemias, acute leukaemias and (acute) lymphoblastic leukaemias, commonly abbreviated to ALL / LL, are broadly comparable as ALLs comprise by far the majority of acute leukaemias, and acute leukaemias, in turn, are the most common form of childhood leukaemia.

The most recent systematic worldwide review of childhood cancers was published in 1998. A comparison with this review shows that the leukaemia incidence rates in the under-15s in Germany can be regarded as typical for a Western country.

For Europe, a review of data to 1997 is available. The different incidence rates within Europe may be partly attributable to differences in diagnostic techniques and recording, but may also be caused by lifestyle differences. In 1978-1997, the childhood leukaemia incidence rates in Europe increased significantly by 0.6 % year on year, with a significant increase of 0.7 % in West Germany. This is presumably caused by changes in lifestyle resulting from greater affluence, with more older mothers and lone children, for example.

When a greater than expected number of cases of a particular disease is observed within a given geographical area or period of time (= aggregation in space and/or time), the question which arises is whether this is a random occurrence or a "cluster". The term "cluster" is used often and very readily in relation to rare diseases such as childhood leukaemia, but generally without any clear definition of what it means. Put simply, it can be defined as meaning that there is a general tendency towards uncommon increases (aggregations), but it may also denote the active search for uncommon aggregations. So can any trend towards uncommon aggregations be observed in space and/or time in the case of childhood leukaemias (particularly LL)? Based on current evidence, this question can be answered as follows: "Probably not, and if at all, then weakly and only in a very small area".

4 Specific epidemiological studies on the role of ionising radiation in childhood leukaemia

For radiobiological reasons, it can generally be assumed that a foetus or very young child is more sensitive to radiation exposure than an adult. There are three main reasons for this:

1. Foetal and juvenile tissues display much higher rates of cell proliferation than adult tissue.

2. A factor of particular relevance to leukaemia is that in early post-natal life (i.e. in infants and young children), the bones – especially peripheral bones – contain more active red bone marrow than adult bones, increasing the risk of leukaemia.

As a consequence, under identical conditions, exposure will deliver significantly greater radiation doses – around 25 % to 30 % higher – to the bone marrow of infants than to adults.

3. When considering the whole-life risk after radiation exposure in childhood, it must be borne in mind that lifespan also plays a role: if initiated in childhood, a cancer has a much longer timeframe in which to become clinically manifest. This is an important factor as a rule, but is obviously not relevant here, as this paper focuses solely on childhood leukaemias.

In relation to the increased risk of contracting leukaemia in early childhood as a result of exposure to ionising radiation, three types of exposure are considered relevant: preconception parental exposure, *in utero* (pre-natal) exposure, and exposure early in life.

In the context of medical radiation exposure, a distinction must be made between: 1) *in utero* (pre-natal) exposure to radiation from diagnostic procedures performed on the mother during pregnancy; 2) post-natal exposure from diagnostic procedures; and 3) post-natal exposure during therapeutic interventions. For those exposed pre-natally, various studies report increased relative risks of 1.2 to 1.5, equivalent to a 20-50 % increase in risk compared with a non-exposed foetus. For post-natal x-ray examinations, figures of ≈ 1.0 are reported, indicating that there is no increased risk of leukaemia associated with post-natal X-rays. Overall, the risk following post-natal exposure is therefore lower than that following *in utero* exposure. However, it must be borne in mind that the studies on post-natal x-ray examinations were performed more recently than the studies on pre-natal exposure, so the radiation doses administered were lower due to advances in x-ray technology. Multimodal treatment, mainly with polychemotherapy, and the possibility of a genetic predisposition to other cancers mean that risk estimates for therapeutic irradiation are unreliable.

With regard to occupational radiation exposure in parents, one issue under discussion is whether irradiation causes mutations in the father's germ cells which are passed on to the child and manifest as an increased number of leukaemia cases ("Gardner hypothesis"). However, there is no scientific evidence for this hypothesis.

No firm conclusions can be drawn from the available studies about a possible association between childhood leukaemia and exposure of the parents/child to natural radiation, especially radon in the home. No increased risk has been reported for civilisation-related radiation exposure of parents from above-ground nuclear weapon tests.

5 Leukaemia risk from ionising radiation

Findings relating to the risks associated with preconception parental exposure are controversial and, according to current knowledge, do not provide a sufficiently reliable basis for assessing risk. That being the case, this paper only assesses the risks arising from *in utero* exposure and exposure early in life.

UNSCEAR[a] (2006) and ICR[b] 103 (2007) find strong evidence that exposure of the foetus to radiation *in utero* causes an increased risk of cancer in childhood (< 15 years of age). ICRP 103 (2007) does not include any specific risk estimates for childhood leukaemias. It merely states that the risk for leukaemia in children and juveniles is around three times higher than the adult risk.

A smaller body of data is available for assessing the risk from post-natal exposure than for *in utero* exposure. Here too, most studies focus on exposure resulting from x-ray examinations. Overall, there are indications that the risk of childhood leukaemia is lower for post-natal X-ray exposure than for *in utero* X-ray exposure. Based on the available data, UNSCEAR (2006) and ICRP 103 (2007) conclude that there is a decline in relative risk with increasing age.

Overall, based on *in utero* exposure for children and juveniles in the entire age range up to 15 years, it may be assumed that the excess relative risk per gray (ERR/Gy) is roughly 40. This produces an extremely low doubling dose of around 25 mGy.

6 Epidemiological studies on childhood leukaemia in the vicinity of nuclear power plant sites

By 1999, a number of ecological studies had been performed among children and juveniles under the age of 15. Several of these studies found evidence of a slightly increased incidence of leukaemia in children under 5 years of age living in the vicinity of a nuclear power plant. A comprehensive analysis of these data showed that the reported increase was limited to certain individual sites.

The Epidemiological Study on Childhood Cancer in the Vicinity of Nuclear Power Plants (KiKK Study) confirms the findings of these earlier studies. It found a statistical correlation between the proximity of a child's residence to the nearest nuclear power plant, at the time of diagnosis, and the child's risk of contracting cancer. There was a significantly increased risk of leukaemia, for children younger than five, within

[a] United Nations Scientific Committee on the Effects of Atomic Radiation

[b] International Commission on Radiological Protection

a 5 km radius around German nuclear power plants, relative to the risk in the outer areas around the relevant study areas. However, the study does not make any inference on the risk factors which might explain this correlation.

Conflicting with the findings of the KIKK Study in Germany, more recent studies carried out in France and the United Kingdom found no evidence of increased leukaemia risks, in children up to the age of 5, in the vicinity of nuclear power plants (within a 5 km radius).[a] To date, no conclusive explanation for the inconsistent results has been presented. The additional radiation exposure caused by nuclear power plants is lower, by a factor of considerably more than 1,000, than the radiation exposure that could cause the risks reported by the KiKK Study.

7 Other risk factors for leukaemia

Many other factors are suspected of triggering childhood leukaemia. These suspicions are mainly based on epidemiological studies. In most cases, however, the data situation remains highly inconsistent: this is because the studies are often based on populations that are too small, the individual leukaemia subtypes are not considered separately, or exposure information is imprecise.

Many different chemicals have been discussed as possibly triggering childhood leukaemia following *in utero* exposure. The most reliable data currently available relate to pesticide exposure, for which increases in leukaemia incidence rates have consistently been observed. It is suspected that post-natal exposure to various chemicals and drugs may also be a factor, but the data currently available do not provide a consistent picture. Based on the findings of several epidemiological studies, the IARC concludes that ELF magnetic fields might be associated with leukaemogenesis, but here too, the available data are contentious, one reason being that there is no known biological mechanism that could explain the epidemiological data.

Two of the main hypotheses under discussion suggest that the immune system plays a key role in leukaemogenesis. Kinlen's hypothesis on population mixing postulates that the large influx of labour migrants from other regions into previously isolated populations, as occurs when new major industries are established, could trigger an increase in leukaemia. According to this hypothesis, a large influx of (mainly urban) newcomers into a rural area previously unexposed to a specific infectious agent could trigger an epidemic of the infection and thus cause an aggregation of rare complications such as leukaemia. This hypothesis appears to be supported by the fact that increases in childhood leukaemia incidence rates have indeed been observed following

[a] The COMARE 11th Report and the Swiss CANUPIS Study were not published until after the present volume was finalised and therefore could not be considered.

the establishment of various large-scale projects. However, one argument against this hypothesis is that it has not yet been possible to identify the postulated infectious agent.

According to Greaves' "delayed infection" hypothesis, the pathogenesis of leukaemia is a two-stage event. As the first event, the expansion of B-cell precursors during pregnancy causes a preleukaemic cell to develop. Following an immune stress such as a common infection in children whose immune system development has been delayed, perhaps due to lack of social contact or overzealous hygiene, the immune system overreacts, boosting the number of preleukaemic cells and thus increasing the probability that the second mutation which is necessary for the further development of leukaemia will occur in one of these cells (second hit). This hypothesis may explain the increased risk of childhood leukaemia observed with factors associated with affluence (and hence higher levels of hygiene), as well as the consistently observed protective effect of frequent social contact in early childhood, provided, for example, by early day care in crèches or nurseries.

Molecular changes in preleukaemic and leukaemic cells can also provide information about risk factors. Structural chromosomal aberrations (such as translocations) are induced by DNA double-strand breaks, for which there may be various triggers. There are increasing signs that various factors may be at play here, depending on the leukaemia subtype. These may be endogenous factors (e.g. faulty recombination) or exogenous factors (e.g. food ingredients that block certain enzymes, or environmental noxae that cause strand breaks). There is thus a growing suspicion that the subgroups of the various leukaemia types differ not only in terms of prognosis and response to certain types of treatment but also in their pathogenesis.

8 Genetic predisposition to childhood leukaemia

Susceptibility to childhood leukaemias is influenced by genetic factors. A number of inherited/genetic disorders and congenital syndromes are associated with a substantially increased incidence of childhood leukaemias; examples are Down's syndrome, ataxia telangiectasia, Bloom's syndrome and neurofibromatosis type 1. Overall, however, only a very small percentage of children with leukaemia are affected by these underlying chronic conditions. Variants in the genes affected by inherited disorders may also be significant in sporadic cases (i.e. those not associated with a discernable familial aggregation); the same applies more generally to variants in genes whose products have a function in cancer-relevant metabolic pathways. Examples of candidate genes for which associations between specific variants and an increased incidence of childhood leukaemia have been found in recent years include those involved in folate metabolism and in detoxification of carcinogens. There is also a growing body of evidence to suggest that variants in immune system genes are significant. The findings of genome-wide association studies may well provide further information about relevant genetic functions in future.

9 Statement by the Commission on Radiological Protection (SSK)

The association between high doses of ionising radiation and leukaemia is well established; convincing evidence of this link, based on comprehensive epidemiological studies, has been available for some time. However, as with solid cancers, the influences of low-dose sources on leukaemia induction remain unclear. As the effects are very slight and there is some variability in the spontaneous frequencies, the leukaemia incidence possibly caused by ionising radiation does not differ significantly from the spontaneous rate. Hence it is also unclear whether exposure to a few millisieverts of ionising radiation causes childhood leukaemia. In any event, the risk is low.

A major difficulty which arises when considering the possible association between ionising radiation and childhood leukaemia is that the causes and mechanisms of leukaemogenesis in children are largely unknown. What is certain is that several mutations in or of the genetic material are needed, and it is clear that a whole range of factors can trigger leukaemia or may at least play a role in its induction.

In order to explain the mechanisms associated with leukaemogenesis, cooperation between scientists from many disciplines is essential. Epidemiologists, geneticists, haematologists, immunologists, molecular biologists, radiation biologists and toxicologists have a particularly important role to play here. Only an interdisciplinary approach is likely to prove successful over the medium to long term.

Efforts must also be made to promote international cooperation, as very large cohorts are required for some studies. This applies particularly when subtype stratification is undertaken. A focus on leukaemia subtypes is important for two reasons. Firstly, clinical experience has shown that in order to achieve the best possible outcomes, the various subtypes cannot all be treated in the same way. Secondly, there are indications that different triggers may cause different subtypes and that the mechanisms of subtype induction also vary. Preliminary steps towards international cooperation have already been initiated (Ziegelberger et al. 2011).

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Ionising Radiation and Childhood Leukaemia (Revision of SSK Volume 29)

Statement by the German Commission on Radiological Protection: Scientific Reasoning

Adopted at the 250th meeting of the German Commission on Radiological Protection on 29/30 September 2011

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Content

1 Introduction

Various studies have found a correlation between the risk of developing childhood leukaemia and the proximity of the home to the nearest nuclear power plant (NPP). However, radiation dose estimates and measurements carried out in the vicinity of these plants show that the doses are so low, by orders of magnitude, that they cannot explain the excesses observed in some cases. In addition, at least some of the studies found increased frequencies of childhood leukaemia in the vicinity of planned sites of nuclear power plants and pre-operational nuclear power plant sites, suggesting that factors other than exposure to ionising radiation are significant in these cases.

The greatest difficulty arising at present when interpreting the available data is that the mechanisms of leukaemia induction and development in children are unknown. However, it seems likely that as with solid cancers, the development of leukaemias is a multistep process, and that the various steps are not necessarily caused by the same agent. It is therefore highly probable that leukaemia development is a multifactorial process. This makes it more difficult to conduct epidemiological studies, as the contributions of the various individual factors may be small and all the relevant factors may have to interact in order to cause leukaemia. There are strong indications that the first step, at least, may be established during pregnancy, especially in children younger than five.

The present volume, which replaces Volume 29 of the Publications of SSK (SSK 1994), reviews the current scientific knowledge about the development of childhood leukaemias, both in general terms and in relation to ionising radiation in particular, in the fields of molecular biology, immunology and epidemiology, and considers various risk factors. The reason why this paper considers not only ionising radiation but other factors as well reflects the fact that as described above, the development of childhood leukaemias is a multifactorial process. The many gaps in our scientific understanding of how leukaemias develop in childhood can only be identified by adopting a comprehensive approach to this issue.

2 Childhood Leukaemia: Medical Aspects

Leukaemia (hyperleukocytosis, “blood cancer”) is a collective term for malignant neoplasms of stem cells in the haemopoietic (= blood-forming) or lymphatic system. Leukaemias are characterised by abnormal proliferation and development of leukocytes and their precursors, which crowd the bone marrow and affect blood-forming cells, and are often also present at elevated levels in peripheral blood. The cancerous cells can also affect the lymph nodes, and can spread to the spleen and other organs. The main symptoms are anaemia, caused by a lack of red blood cells (erythrocytes), bleeding due to thrombocytopenia, and immune deficiency due to the lack of functioning leukocytes. These cause pallor and fatigue, frequent bleeding, susceptibility to bacterial infections and therefore bouts of fever, functional impairment of affected

organs, and pain. Depending on the course of the disease, a distinction is made between acute and chronic forms. Leukaemia was first described by Rudolf Virchow in 1845; acute myeloid leukaemia was first described by Nikolaus Friedreich in 1847. It was recognised as a distinct pathological entity in 1878.

2.1 Classification

The clinical classification of leukaemias is based on morphological and immunological features of the affected cells, with additional cytogenetic and molecular biological characterisation. A distinction is made between myeloid (ML) and lymphoid leukaemias (LL), depending on the type of cell affected. Myeloid leukaemias originate from granulocytes, erythrocytes and thrombocytes. Lymphoid leukaemias affect the lymphocytes and their precursor cells. The classification systems are described in detail in Section 3.1.

There is reason to suspect leukaemia if changes in the (differential) blood count can be observed. Precise classification must be based on a bone marrow biopsy.

The main types of leukaemias occurring in children and adolescents are:

- acute lymphoblastic leukaemia (ALL): a diagnosis of ALL is indicated when malignant lymphoblasts comprise more than 25 % of nucleated cells in bone marrow; at the time of diagnosis, the figure is generally above 80 %;

- acute myeloid leukaemia (also known as acute myelogenous leukaemia) (AML): a diagnosis of AML is indicated by demonstrating involvement of more than 20 % of the bone marrow by monoblasts or myeloblasts. A malignant disorder of red cell precursors or platelets, as a subtype of AML, is classified as erythroleukaemia or megakaryoblastic leukaemia. Chromosomal changes (especially reciprocal translocations) are of particular significance for the patient's prognosis.

- chronic myeloid leukaemia (CML): this is characterised by an elevated white cell (leukocyte) count (mean: 240 000 leukocytes/µL), a relatively low percentage of myeloblasts (below 15 %) and an increase in mature granulocytes and their precursors. The t(9;22) chromosomal translocation is typically found in more than 90 % of cases. It is known as the Philadelphia chromosome after the place where it was first identified and described.

ALL and AML have numerous subtypes, characterised by distinct gene and protein expression and chromosomal features. For an overview, see, for example, Leitlinien der AWMF (= Guidelines of the German Association of Scientific Medical Societies) (2010), based on Biondi et al. 1992, Bürger et al. 2003, Reinhard et al. 2006 and Van der Does-van den Berg et al. 1992.

Chronic lymphocytic leukaemia (CLL) is classified as a non-Hodgkin's lymphoma of low malignancy. Children and adolescents almost never contract CLL, so it will not be considered further here. CML belongs to a group of diseases known as the myeloproliferative disorders. Rare diseases which are related to CML but are non-malignant and, strictly speaking, therefore should not be classified as leukaemia include polycythaemia vera (PV) – which causes a high number of red blood cells (erythrocytosis) and generally also leukocytosis (a raised white blood cell count) and thrombocytosis (the presence of high platelet counts in the blood) – and essential thrombocythemia (ET), characterised by the overproduction of platelets, mostly with impaired function. In the third revision of the ICD-O (ICD-O-3), polycythaemia vera was recognised and reclassified as a malignant neoplasm. Juvenile myelomonocytic leukaemia (JMML), formerly termed juvenile chronic myeloid leukaemia, is a specific type of leukaemia which is distinct from the myelodysplastic syndromes (MDS). CML is extremely rare in children and will not be considered further here.

There are various specific clinical classification systems, such as the French-American-British (FAB) classification system for AML, first produced in 1976 (Bennett et al. 1976), and the WHO classification scheme (Harris et al. 1999, Vardiman 2009). The classification systems are constantly developing in the light of new scientific knowledge.[a]

2.2 Incidence and course of the disease

In Germany, an average of 1 820 new cases of cancer or benign brain tumour in the under-15s are diagnosed each year (RKI/GEKID 2010, Kaatsch and Spix 2009). The incidence rate is approximately 160 cases per 1 000 000[b] children per year. Around 34 % of these children are diagnosed with leukaemia or a related disease. The incidence rate for all childhood leukaemias in Germany is 55 cases per 1 000 000 children per year. In other words, for every 1 270 newborns, one case of childhood leukaemia is diagnosed before they reach 15 years of age. ALL is the most frequent diagnosis, accounting for 44 cases per 1 000 000 children per year (27 %). It is more than twice as common in the under-4s than in any other age group. AML accounts for 7.4 cases

[a] The International Statistical Classification of Diseases, Injuries and Causes of Death (ICD) is designed to promote international comparability in the collection, processing, classification, and presentation of statistics on diseases and causes of death (see Section 3.1). Using the ICD system, diseases and causes of death are classified in alphanumeric categories. ICD-10, published by WHO/DIMDI (2006 version) (http://www.dimdi.de/static/de/klassi/diagnosen/icd10/index.htm) and the preliminary version of ICD-10-GM (special preliminary version 2011 on "Leukaemias and Lymphomas") (http://www.dimdi.de/dynamic/de/klassi/downloadcenter/icd-10-gm/version2011-vorab-leukaemienlymphome/) identify the following main types of leukaemia: plasma cell leukaemia (C90.1), lymphoid leukaemia (C91), myeloid leukaemia (C92), monocytic leukaemia (C93) and other leukaemias (C94, C95).

[b] Conventionally, incidence rates of cancer are expressed as cases per 100 000 person-years. For childhood cancers, the rate is often expressed per million, due to the small number of cases.

of malignancy per 1 000 000 children per year (approximately 5 %), occurring most frequently in the under-2s. The median age at diagnosis in the under-15s is 4.8 years for ALL and 5.8 years for AML (RKI/GEKID 2010, AWMF 2010, DKKR 2009). During the first year of life, ALL affects boys and girls in roughly equal numbers, but later on, it is more common in boys than in girls (RKI/GEKID 2010, DKKR 2009). Philadelphia chromosome-positive CML is not unknown in children and adolescents but occurs much more rarely than in adults, with around 20 cases diagnosed in the under-18s in Germany per year (Suttorp 2005).

A 10- to 20-fold increased risk of leukaemia in children with Down's syndrome is reported compared with children without trisomy 21 (Linabery et al. 2006, Robison 1992, Ross et al. 2005), resulting in an incidence of 1:100. In these children, there is a predominance of acute megakaryoblastic leukaemia (AMKL) during the first years of life. Compared with children without Down's syndrome, however, children with trisomy 21 and AML generally respond better to chemotherapy, their prospects of cure and survival are much higher, and relapses are less common. Increased incidence of leukaemia is also associated with a number of other syndromes (see Chapter 7).

Genetic mutations of relevance to paediatric ALL and AML or fusion genes in blood cells commonly already exist *in utero* in children with leukaemia (see Section 6.6). However, only a fraction of children with the fusion gene or genetic change go on to develop leukaemia. This indicates that additional post-natal events are needed for leukaemia to develop. Very little is known at present, however, about the sequence of genetic events, or, indeed, about the specific event responsible for the sudden onset of leukaemia.

Neoplastic transformation of stem/precursor cells is followed by clonal expansion, forming an expanding clone of neoplastic cells through cell division. Acute leukaemias are generally characterised by a progressive accumulation of immature precursors of blood cells (blasts) in the bone marrow, progressing rapidly and often appearing suddenly without an obvious prodrome (Pui et al. 2008).

2.3 Treatment and prognosis

Childhood leukaemia is generally treated by employing tested risk-adapted polychemotherapy protocols (AWMF 2010, Schrappe 2008, Kaspers and Creutzig 2005, Suttorp 2008). The role of new targeted therapies (biologics) such as tyrosine kinase inhibitors in ALL and CML is still being evaluated (Gruber et al. 2009, Kaspers and Creutzig 2005, Suttorp 2008).

ALL is associated with a favourable prognosis, with long-term[a] disease-free survival of 60-90 %, depending on type. With standard anthracycline/Ara-C regimens, a rate of complete remission of 60-80 % can also be achieved for AML, although long-term disease-free survival with no relapse is as low as 20-30 % (Shipley and Butera 2009). The introduction of the tyrosine kinase inhibitor imatinib (IM) has resulted in estimated long-term survival rates close to 90 % for paediatric patients (Suttorp 2008).

2.4 Acute lymphoblastic leukaemia (ALL)

Clinical factors (age, initial WBC count) play a role in risk stratification in childhood ALL; on their own, however, they are insufficiently specific. The main indicator of a high risk of relapse is a poor response to a prednisone prophase. An overview of the most important cytostatic drugs can be found in current guidelines (e.g. AWMF 2010). Generally, a selection of appropriate substances is administered in a specific sequence, based on high-quality controlled treatment studies. For example, in the ALL-BMF 90 study (Schrappe et al. 2000), the following treatment phases were conducted:

I. 5-week induction therapy followed by a 4-week consolidation: various drugs

II. an 8-week extra-compartment therapy: 6-mercaptopurine (MP) and methotrexate (MTX)

III. 7-week re-induction therapy: various drugs

IV. maintenance therapy for up to 24 months post-diagnosis: MP (or thioguanine), MTX.

Maintenance therapy up to a total treatment duration of 24 months is a standard component of all treatment protocols. Treatment is based on monitoring of leukocyte and lymphocyte counts, the aim being to achieve a leukocyte count of 2000-3000/mm^3 and a lymphocyte count >300 mm^3.

[a] Originally, the review period was just five years. As the results of long-term monitoring are now available, this timespan has been extended to 15 years and more.

Supportive care regimens are also required, such as blood and plasma transfusions, infusion therapy, and short-term intensive treatment for sepsis in some circumstances. Parenteral or special nutrition and pain therapy may also have a role to play. Integrated clinical monitoring of patients, as well as psychosocial support, are required throughout treatment. The long-survival rate is currently around 85 %.

Allogeneic hematopoietic stem cell transplantation

This is only performed after a relapse in second remission or when there is clearly a high risk of relapse 3-4 months after remission is achieved. Potential donors are HLA-identical siblings or HLA-matched related or unrelated donors. Allogeneic bone marrow or stem cell transplantation may ultimately lead to a cure for many patients.

Treatment for CNS invasion: CNS irradiation

This is indicated solely for subclinical invasion (<5 cells/mm^3 liquor) in patients with a higher risk of relapse. If invasion is manifest, low-dose CNS irradiation is generally performed, which several studies have shown to be very effective (AWMF 2010).

As a general principle, children should not undergo CNS irradiation during the first year of life. All patients must also undergo appropriate intrathecal and systemic treatment (MTX).

2.4.1 Acute myeloid leukaemia (AML)

The standard therapeutic approach for AML patients is high-dose polychemotherapy. The treatment for AML consists of intensive induction therapy, which induces remission in two-thirds of patients, followed by consolidation and intensification for a period of 4-6 months. Maintenance therapy and CNS irradiation continue to be controversial. Stem cell transplantation is no longer performed in first remission, irrespective of prognosis group.

I. induction therapy: cytarabine (Ara-C), anthracycline, possibly others (etoposide)

II. post-remission therapy: 3-4 treatment blocks, often with the same drugs.

Intrathecal Ara-C, MTX or a combination with hydrocortisone are used for CNS prophylaxis or treatment. Generally, CNS irradiation (total dose 18 Sv) is recognised as being appropriate when CNS invasion is manifest, but prophylactic irradiation remains a controversial issue.

Tables 2.1 and 2.2 show the prognostic factors for ALL and AML (based on AWMF 2010, Onciu 2009).

Table 2.1: Prognostic factors for ALL (based on AWMF 2010, Onciu 2009)

Prognostic Factors	Favourable	Unfavourable
Age at diagnosis[a]	1 - 5 years	<1, ≥10 years
WBC	<20 000/µl	>100 000/µl
Immunophenotypic features	Early pre-B	T-cells
Ploidy / DNA index	Hyperdiploidy (>50 chromosomes) / ≥1,16	Hyperdiploidy (<46 chromosomes) / <1,0
Genetic alterations	t12;21 with *TEL-AML-1* fusion gene; t15;17, inv16, t8;21; trisomy 4, 10, 17;	t4;11 with *MLL-AF4* fusion gene, t9;22 with *BCR-ABL* fusion gene, t6;9; trisomy 8, aberrations in chromosome 5,7; complex aberrations
Clinical response after 7 days of prednisone (prophase)	<1 000 blasts/µl	≥1 000 blasts/µl
Clinical response to initial induction therapy (4-6 weeks)	<5 % blasts	>5 % blasts
Evidence of minimal residual disease (MRD)	No minimal residual disease after 5 weeks	Minimal residual disease-positive (>1 000 cells) after 12 weeks

[a] *Advani et al. 2009, Ribera and Oriol 2009*

Table 2.2: Prognostic factors for AML (based on AWMF 2010, Onciu 2009)

Prognostic Factors	Favourable	Unfavourable
Disease	Acute promyelocytic leukaemia (APL)	
Cytogenetic abnormality	t15;17, t8;21, inv16	del5,7, complex aberrations

In Germany, patients with the following conditions are classed as standard-risk patients:

- AML with/without maturation or favourable cytogenetics
- Acute promyelocytic leukaemia (APL)
- Acute myelomonocytic leukaemia with eosinophilia
- >5 % blasts on day 15
- *FLT3-IDT* negative (with the exception of AML in patients with Down's syndrome).

All other types fall into the high-risk group (Creutzig et al. 1999).

2.4.2 Chronic myeloid leukaemia (CML)

CML is a stem cell disease and therefore cannot be cured with conventional chemotherapy. The initial chronic phase (stable disease) generally lasts 5-6 years. This is followed by a poorly defined accelerated phase (5-10 months) and then the terminal phase, or blast crisis, which is similar to acute leukaemia, with survival of around three months. Hematopoietic (= blood-forming) stem cell transplantation (SCT) from a related or unrelated donor is the only proven cure. This procedure is beset with numerous acute and chronic risks but leads to long-term recovery in 60-90 % of paediatric cases (Suttorp et al. 2009). Since 1999, the advent of the tyrosine kinase inhibitors such as imatinib has revolutionised the treatment of CML in adults and has extended the duration of the chronic phase to an estimated 20 years. Although experience with imatinib in paediatrics is still limited, response rates in children are similar to those observed in adults (Millot et al. 2006). Transplantation is therefore indicated as a second-line therapy for patients with imatinib-resistant or intolerant CML (Bacher et al. 2009).

Further reading:

Eden T.: Aetiology of childhood leukaemia. Cancer Treat Rev 36(4):286-297, 2010 [Epub ahead of print; doi:10.1016/j.ctrv.2010.02.004]

Stanulla M.; Schrappe M.: Treatment of childhood acute lymphoblastic leukemia. Semin Hematol. 46:52-63, 2009

Stiller C. A.; Parkin D. M.: Geographic and ethnic variations in the incidence of childhood cancer. Br Med Bull. 52:682-703, 1996

Stiller C. A.: Epidemiology and genetics of childhood cancer. Oncogene 23:6429-6444, 2004

3 Descriptive Epidemiology

3.1 Epidemiological classification of childhood leukaemia, nomenclature, abbreviations

There are various classification systems, based on clinical or epidemiological criteria. A clinical classification system (such as FAB, see Chapter 2) supports risk stratification during treatment, whereas a scheme based on epidemiology supports long-term international standard diagnostic classification. The terminology relating to childhood leukaemias is not fully standardised in the international literature in the field of epidemiological research. Often, the underlying classification system is not specified, making it more difficult to compare results.

Relevant classification systems are the **ICD**, the **ICD-O** and the **ICCC**.

International Classification of Diseases (ICD): the scope of this classification system includes all diseases and conditions. In relation to cancer, the ICD's approach is based on topography and, in terms of epidemiology, refers to systemic oncological diseases in relatively broad terms. The ICD usually forms the basis for cancer reporting by general cancer registries.

The ICD-O (O = oncology) is a sub-division of the ICD and relates specifically to cancer epidemiology. The ICD-O is a dual-axis classification providing coding systems for both topography and morphology. A disease is generally characterised using a combination of the two codes. The last digit of the morphology code is the behaviour code, which indicates whether a tumour is benign (0); uncertain (1); in situ (2); or malignant (3). The topography code is based closely on the ICD. For the systemic diseases which are the sub-

ject of this paper, topography is not stated or is irrelevant for disease characterisation.

The International Classification of Childhood Cancer (ICCC) is based on the International Classification of Diseases for Oncology (ICD-O). It is the standard for reporting on malignant diseases in childhood and adolescence and takes account of the specific characteristics of disease in these age groups. Childhood cancer is classified with an emphasis on morphology rather than on primary site (topography). Its main areas of application are cancer registration and epidemiological studies of childhood cancer.

The ICD and ICD-O classification systems are published by the World Health Organization (WHO)[a]. Country-specific versions of these two systems also exist (see also Section 2.1). The ICCC was developed by a working group set up by the International Agency for Research on Cancer (IARC)[b]. The ICD is revised periodically and is currently in its tenth revision. This is then followed by the revision of the ICD-O, currently in its third revision and, on that basis, the ICCC (the first version of the ICCC, which was based on ICD-O-2, was followed by the current version, i.e. ICCC-3, which is based on ICD-O-3) (Kramarova and Stiller 1996, Steliarova-Foucher et al. 2005a) (see Table 3.1). Generally, several years elapse between the time of publication to implementation and use. Recoding of a dataset, e.g. an entire register, from one version to the next is an extremely labour-intensive process. Apart from the ICCC, details of the history of the classification systems can be obtained from the publications produced by the German Institute of Medical Documentation and Information (DIMDI)[c], which publishes the German versions of the ICD.[d] Epidemiological studies of malignant diseases in children and adolescents from the 1990s and early 21st century are generally based on ICD-O-2/ICCC (Kramarova and Stiller 1996), with more recent publications based on ICD-O-3/ICCC-3 (Steliarova-Foucher et al. 2005a). A specific feature of ICCC-3 compared with ICCC is that it offers the option of an additional, more refined sub-division, known as “extended classification”.

A single morphological code generally covers a wide range of diagnosis descriptions, with this diversity having medical and historical causes. In each case, the published ICD-O therefore identifies one specific term as the “preferred term”, which will be used in this paper.

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[a] World Health Organization (WHO): the authority for health within the United Nations system.

[b] The International Agency for Research on Cancer is part of the World Health Organization (WHO).

[c] German Institute of Medical Documentation and Information = *Deutsches Institut für Medizinische Dokumentation und Information*, http://www.dimdi.de/static/de/index.html.

[d] In order to ensure international comparability, the international classification and nomenclature are used exclusively and at all levels in the German Childhood Cancer Registry.

In the mid-1990s, the diagnostic classification of lymphoma was revised, which may have led to a number of minor shifts and reassignments between some subtypes of non-Hodgkin's lymphoma and lymphoid leukaemia (Harris et al. 1994). This possibly affected up to 5 % of ALL cases (= acute lymphoblastic leukaemia, used as a synonym for lymphoid leukaemia, see below) and 20 % of non-Hodgkin's lymphoma (NHL) in the 1980s (Coebergh et al. 2006). However, analyses undertaken during the preparation of the 2009 Annual Report of the German Childhood Cancer Registry (Kaatsch and Spix 2009) found no evidence of numerically relevant shifts for Germany from 1987 onwards.

Clinical assignment to an ALL or NHL treatment protocol is based on rather different criteria than epidemiological classification. Over the last 10 years, around 2 % of patients in Germany whose diseases were assigned epidemiologically to lymphoid leukaemia (LL) (ICCC-3 I(a), see below) were treated according to an NHL protocol, and around 6 % of patients whose diseases were classified epidemiologically as NHL (ICCC-3 II(b)) were treated with an ALL protocol (source: German Childhood Cancer Registry (see also Section 2.3)).

Table 3.1: Classification of leukaemias according to ICD-O-2 and ICCC (Kramarova and Stiller 1996; tabular overview: German Childhood Cancer Registry)

	ICD-O-2 codes	
Diagnostic group	**Morphology**	**Topography**
I LEUKAEMIA		
(a) Lymphoid leukaemia	9820-9827, 9850	
(b) Acute non-lymphocytic leukaemia	9840, 9841, 9861, 9864, 9866, 9867, 9891, 9894, 9910	
(c) Chronic myeloid leukaemia	9863, 9868	
(d) Other specified leukaemias	9830, 9842, 9860, 9862, 9870-9890, 9892, 9893, 9900, 9930-9941	
(e) Unspecified leukaemias	9800-9804	

Preferred Term ICD-O-2	Morphology code ICD-O-2
Lymphoid leukaemia, NOS	9820/3
Acute lymphoblastic leukaemia, NOS	9821/3
Subacute lymphoid leukaemia	9822/3
Chronic lymphocytic leukaemia	9823/3
Aleukemic lymphoid leukaemia	9824/3
Prolymphocytic leukaemia, NOS	9825/3
Burkitt's cell leukaemia	9826/3
Adult T-cell leukaemia/lymphoma	9827/3
Lymphosarcoma cell leukaemia	9850/3
Erythroleukaemia	9840/3
Acute erythremia	9841/3
Acute myeloid leukaemia	9861/3
Aleukemic myeloid leukaemia	9864/3
Acute promyelocytic leukaemia	9866/3
Acute myelomonocytic leukaemia	9867/3
Acute monocytic leukaemia	9891/3
Aleukemic monocytic leukaemia	9894/3
Acute megakaryoblastic leukaemia	9910/3
Chronic myeloid leukaemia, NOS	9863/3
Chronic myelomonocytic leukaemia	9868/3
Plasma cell leukaemia	9830/3
Chronic erxthremia	9842/3
Myeloid leukaemia, NOS	9860/3
Subacute myeloid leukaemia	9862/3
Basophilic leukaemia	9870/3
Eosinophilic leukaemia	9880/3
Monocytic leukaemia	9890/3
Subacute monocytic leukaemia	9892/3
Chronic monocytic leukaemia	9893/3
Mast cell leukaemia	9900/3
Myeloid sarcoma	9930/3
Acute panmyelosis	9931/3
Acute myelofibrosis	9932/3
Hairy cell leukaemia	9940/3
Leukemic reticuloendotheliosis	9941/3
Leukaemia, NOS	9800/3
Acute leukaemia, NOS	9801/3
Subacute leukaemia, NOS	9802/3
Chronic leukaemia, NOS	9803/3
Aleukemic leukaemia, NOS	9804/3

NOS: Not otherwise specified

The nomenclature customarily used in general cancer registries, based on ICD, is broadly in line with that used by the ICCC (see Table 3.2).

Table 3.2: Nomenclature of leukaemias in ICD-10 (excerpt)

ICD-10 (2-digit)	Selected subtypes (3-digit)	Name (English/German)	Approximate ICCC equivalent
C91	C91.0	Lymphoid leukaemia / *Lymphatische Leukämien* Acute lymphoblastic leukaemia / *Akute lymphatische Leukämie*	I (a)
C92 C93	 C92.0 C92.1	Myeloid leukaemia / *Myeloische Leukämien* AML CML Monocytic leukaemias / *Monozyten-Leukämie*	I (b), I(c)
C94		Other leukaemias of specified cell type / *Sonstige näher bezeichnete Leukämien*	I (d)
C95		Leukaemia of unspecified cell type / *Sonstige nicht näher bezeichnete Leukämien*	I (e)

Class I(a), which is correctly termed "lymphoid leukaemia" (LL), is often – for historical reasons – also termed "acute lymphoblastic leukaemia" (ALL) (this applies to the ICCC and also to ICCC-3, see below). With very rare exceptions, I(a) includes only acute forms of lymphoid leukaemia in children. ICCC I(b) (acute non-lymphocytic leukaemia – ANLL) was generally termed akute *myeloische Leukämie* (= acute myeloid leukaemia (AML)) in the German language area even prior to the introduction of ICCC-3; see I(b) in Table 3.3 below.

Table 3.3: Classification according to ICD-O-3 and ICCC-3 (Steliarova-Foucher et al. 2005a; tabular overview: German Childhood Cancer Registry)

	ICD-O-3 codes	
Diagnostic group	**Morphology**	**Topography**
I LEUKAEMIAS, MYELOPROLIFERATIVE AND MYELODYSPLASTIC DISEASES		
(a) Lymphoid leukaemias	9820, 9823, 9826, 9827, 9831-9837, 9940, 9948	
(b) Acute myeloid leukaemias	9840, 9861, 9866, 9867, 9870-9874, 9891, 9895-9897, 9910, 9920, 9931	
(c) Chronic myeloproliferative diseases	9863, 9875, 9876, 9950, 9960-9964	
(d) Myelodysplastic syndrome and other myelopro-liferative diseases	9945, 9946, 9975, 9980, 9982-9987, 9989	
(e) Unspecified and other specified leukaemias	9800, 9801, 9805, 9860, 9930	

Preferred Term ICD-O-3	**Morphology code ICD-O-3**
Lymphoid leukaemia, NOS	9820/3
B-cell chr. lymph. leuk./small lymphocytic lymphoma	9823/3
Burkitt cell leukaemia	9826/3
Adult T-cell leukaemia/lymphoma (HTLV-1 pos.)	9827/3
T-cell large granular lymphocytic leukaemia	* 9831/1
Prolymphocytic leukaemia, NOS	9832/3
Prolymphocytic leukaemia, B-cell type	9833/3
Prolymphocytic leukaemia, T-cell type	9834/3
Precursor cell lymphoblastic leukaemia, NOS	9835/3
Precursor B-cell lymphoblastic leukaemia	9836/3
Precursor T-cell lymphoblastic leukaemia	9837/3
Hairy cell leukaemia	9940/3
Aggressive NK-cell leukaemia	9948/3
Acute myeloid leukaemia, M6 type	9840/3
Acute myeloid leukaemia	9861/3

Acute promyelocytic leuk.,t(15;17)(q22;q11-12)	9866/3
Acute myelomonocytic leukaemia	9867/3
Acute basophilic leukaemia	9870/3
Ac. myelomonocytic leuk. w. abn. mar. eosinophils	9871/3
Acute myeloid leukaemia, minimal differentiation	9872/3
Acute myeloid leukaemia without maturation	9873/3
Acute myeloid leukaemia with maturation	9874/3
Acute monocytic leukaemia	9891/3
Acute myeloid leuk. with multilineage dysplasia	9895/3
Acute myeloid leukaemia, t(8;21)(q22;q22)	9896/3
Acute myeloid leukaemia, 11q23 abnormalities	9897/3
Acute megakaryoblastic leukaemia	9910/3
Therapy-related acute myeloid leukaemia, NOS	9920/3
Acute panmyelosis with myelofibrosis	9931/3
Chronic myeloid leukaemia, NOS	9863/3
Chronic myelogenous leukaemia, BCR/ABL positive	9875/3
Atypical chronic myeloid leuk., BCR/ABL negative	9876/3
Polycythemia vera	9950/3
Chronic myeloproliferative disease, NOS	9960/3
Myelosclerosis with myeloid metaplasia	9961/3
Essential thrombocythemia	9962/3
Chronic neutrophilic leukaemia	9963/3
Hypereosinophilic syndrome	9964/3
Chronic myelomonocytic leukaemia, NOS	9945/3
Juvenile myelomonocytic leukaemia	9946/3
Myeloproliferative disease, NOS	* 9975/1
Refractory anemia	9980/3
Refractory anemia with sideroblasts	9982/3
Refractory anemia with excess blasts	9983/3
Refract. anemia with excess blasts in transformation	9984/3
Refractory cytopenia with multilineage dysplasia	9985/3
Myelodysplastic syndr. with 5q deletion syndrome	9986/3
Therapy-related myelodysplastic syndrome, NOS	9987/3
Myelodysplastic syndrome, NOS	9989/3
Leukaemia, NOS	9800/3
Acute leukaemia, NOS	9801/3
Acute biphenotypic leukaemia	9805/3
Myeloid leukaemia, NOS	9860/3
Myeloid sarcoma	9930/3

NOS: Not otherwise specified

**: In ICD-O-3, listed only with the behaviour code (1), which indicates that a tumour is uncertain (1). ICCC-3 includes exceptions in the event that the pathologist assigns a behaviour code (3) = malignant.*

Main diagnostic group I (ICCC-3) – in contrast to main diagnostic group I (ICCC) – refers to "leukaemias, myeloproliferative and myelodysplastic diseases" and therefore includes related diseases which are clearly distinct from leukaemia. For epidemiological purposes, diagnostic groups ICCC I(a)-(e) are therefore broadly comparable with ICCC-3 I(a)-(c),(e), and both can be termed **"leukaemias"** or "leukaemia". In epidemiological analyses, **"acute leukaemia"** is generally defined in terms of ICCC I(a),(b) or ICCC-3 I(a),(b), and is usually abbreviated to "ALL" and "AML" (or ALL and ANLL), although they also include a number of rare non-acute forms. Strictly speaking, the diagnostic group "acute leukaemias" would comprise selected morphologies from ICCC-I(a),(b),(d),(e) or ICCC-3 I(a),(b),(e).

Making matters more complicated, MDS (ICCC-3 I(d)) can develop into AML. When ICD-O-2 was valid, MDS was still classed as non-malignant and was not included in the ICCC. Registration only took place once the condition had degenerated into AML. Nowadays, registered cases of MDS which degenerate into AML are recoded using a specific morphology code.

Diagnostic groups I(a) and (b) account for more than 90 % of patients under 15 years of age in the main diagnostic group I, so epidemiological findings for children based on I ("leukaemia") are broadly comparable with findings based on I(a) and (b) ("acute leukaemia").

3.2 Descriptive epidemiology of childhood leukaemia

3.2.1 Leukaemia incidence rates in childhood and adolescence: an international review

The incidence rate is the number of new disease cases occurring in a defined at-risk population over a given time period, and is generally calculated using person-years. Cases, not persons, are counted. In epidemiology, the incidence rate per year is conventionally expressed, and population estimates are used to approximate person-years. The crude incidence rate is calculated by dividing the total number of cases by the total population (total number of person-years). Age-standardised rates are also used: here, the calculation is a weighted average of age-specific rates (see also Table 3.6). Cumulative incidence is not a rate but a measure of risk. It is derived by adding up the age-specific rates. Cumulative incidence for age 0-<15 is generally defined as a newborn's risk of contracting the disease before his or her 15th birthday.

3.2.1.1 Childhood leukaemia: international epidemiology

Whereas for adults, reviews of cancer incidence worldwide are published on a regular basis (IARC: "Cancer Incidence in Five Continents"[a]), the same unfortunately does not apply to childhood cancer. The most recent comprehensive overview of childhood can-

[a] cf. www.iarc.fr

cer worldwide was published in 1998 (Parkin et al. 1998). This international review of childhood cancer incidence is based on 24 selected registries worldwide which, according to the IARC's criteria, present reliable data on childhood cancer incidence. It showed that at that time, the German standardised incidence rates were exactly the same as the median of the other registries for ALL (ICCC I(a)) and AML (ICCC I(b)) (Table 3.4). Incidence rates observed for ALL for some Scandinavian countries can be considered to be rather high; this is in line with the corresponding observation made in the ACCIS project for the Northern Europe region (Coebergh et al. 2006). Overall, the leukaemia incidence rates in the under-15s in Germany can be regarded as typical for a Western country.

Table 3.4: Age-standardised incidence rates of the 24 largest childhood cancer registries by diagnoses: childhood malignancies – total incidence rate (under-15s, per million per year); the periods covered by the various countries/registries vary within the total time period 1980-1995; excerpt from the 1998 Annual Report of the German Childhood Cancer Registry (Kaatsch et al. 1998)

Registry	Childhood malignancies total incidence rate (under-15s) per million per year	ALL incidence rate (under-15s) per million per year	AML incidence rate (under-15s) per million per year
USA, Los Angeles (Hispanic)	161	48	9
New Zealand, non-Maori	159	41	8
Denmark	159	43	8
Sweden	154	40	7
Finland	154	42	5
Norway	152	38	8
USA, SEER (white)	150	38	6
Canada	149	41	6
USA, New York (white)	149	37	7
USA, Greater Delaware (white)	145	37	7
Italy	143	38	8
Australia	142	40	8
Spain	141	33	8
Costa Rica	136	46	9
France	135	32	6
Netherlands	135	31	6
Germany, German Childhood Cancer Registry (GCCR)	134	38	7
Japan, Osaka	133	28	8
Israel, Jews	133	19	5
Hong Kong	132	41	4
Slovakia	129	27	7
Czech Republic	126	28	5
UK, Scotland	125	34	5
UK, England and Wales	122	33	6

Standard: Segi World Standard Population (see Table 3.6);
ALL = acute lymphoblastic leukaemia; AML = acute myeloid leukaemia (I(a) / I(b) based on ICCC)
Incidence rate: average number of new cases per million per year
Age standardisation: weighted average of the age-specific rates using a standard population

3.2.1.2 Descriptive epidemiology of childhood leukaemia in Europe

The Automated Childhood Cancer Information System (ACCIS) project (Steliarova-Foucher et al. 2006a) collected all the available data on cancer in children (<15 years) and adolescents (15-<20 years) in Europe for the period 1978-1997. It covered around half of all childhood cases and around a quarter of all adolescent cases in Europe in this period. The registry data were based on ICCC or were converted centrally. Besides providing a general descriptive overview, the ACCIS Project also aimed to present temporal trends and spatial comparisons within Europe (Kaatsch et al. 2006, Steliarova-Foucher et al. 2005b, Steliarova-Foucher et al. 2006b, Stiller et al. 2006).

The summary evaluations are based on data from the following countries, defined in terms of regions (nc: not comprehensive): British Isles: Ireland, England, Wales, Northern Ireland, Scotland; Eastern Europe: Belarus, Estonia, Hungary, Slovakia; Northern Europe: Denmark, Finland, Iceland, Norway; Southern Europe: Italy (nc), Malta, Slovenia, Spain (nc), Turkey (nc); Western Europe: France (nc), Germany (West Germany to 1990; all of Germany from 1991), Netherlands, Switzerland (nc). Data for the German Democratic Republic to 1989 are included in the "Europe – total" figures, but the GDR is not assigned to any region. The figures for adolescent cases (15 -< 20 years) are based on a much smaller dataset with fewer countries (they exclude Germany, for example).

3.2.1.3 Spatial comparisons in Europe

Table 3.5: Standardised incidence rates for ALL and AML (ICCC I(a),(b)) per million per year in regions of Europe 1988-1997 for children (under 15 years of age) and adolescents (15 -<20 years) (Stiller et al. 2006). The incidence rates for 0-<15, 15-<20 and the most affected age group (ALL: 1-<5, AML: <1) are shown

	Lymphoid leukaemia (mainly acute lymphoblastic leukaemia) ICCC I(a) **Standardised incidence rate per million per year**			**Acute myeloid leukaemia ICCC I (b)** **Standardised incidence rate per million per year**		
Age	Most affected age group 1-<5 years	0-<15 years	15-<20 years	Most affected age group <1 year	0-<15 years	15-<20 years
Europe (total)	65,2	35,9	12,6	13,3	6,5	7,0
British Isles	65,3	35,1	15,3	12,4	6,5	9,2
Eastern Europe	55,2	32,1	8,8	6,5	4,8	6,5
Northern Europe	75,7	39,1	11,5	14,6	6,6	6,8
Southern Europe	71,1	38,2	15,0	14,3	6,1	7,5
Western Europe	65,4	36,4	11,9	15,1	7,0	6,0

Standard: Segi World Standard Population (see Table 3.6);
ALL = acute lymphoblastic leukaemia, AML = non-lymphocytic leukaemia (I(a) / I(b) based on ICCC)
Incidence rate: average number of new cases per million per year
Age standardisation: weighted average of the age-specific rates using a standard population

The regional differences in the incidence rates can partly be explained by differences in diagnostic methods and registration (Table 3.5). What is striking, however, is that the rather lower incidence rates for ALL in Eastern Europe relate specifically to age years 2 and 3. This ties in with general observations that the increases in ALL incidence rates over time have, for some years, mainly been observed in the 1-<5 year age group (Coebergh et al. 2006, McNally et al. 2001, Eden 2010) (see also Section 3.2.1.4 below).

3.2.1.4 Trend analyses in Europe

In 1978-1997, the incidence of leukaemia (ICCC I) among children under 15 years of age in Europe rose by around 0.6 % per year (significant p<0.0001), mainly due to the 0.8 % annual rise in the ALL rate (ICCC I(a)) (significant p<0.0001) and AML incidence (ICCC I(b)) by an (insignificant p=0.11) 0.5 % per year. This is presumably caused by changes in life style resulting from greater affluence, such as an increase in maternal age at delivery, more children without siblings, etc. (Coebergh et al. 2006, Kaatsch et al. 2006, Steliarova-Foucher et al. 2005b).

The increase in leukaemia incidence over time and the higher incidence rates in Southern and Northern Europe in particular, compared with Eastern Europe, mainly relate to the most frequent subtype, precursor B-cell lymphoblastic leukaemia, or "common ALL" (also known as c-ALL, ICD-O-3 morphology 9836/3), which accounts for the majority of cases in the 1-<5 age group.

Researchers in the Czech Republic analysed the changes in leukaemia incidence rates observed in that country during the period 1980-1998 and found an apparent correlation between the observed increase and socioeconomic transition (Hrusak et al. 2002).

3.2.2 Childhood leukaemia in Germany: current figures for diagnostic groups

Most of the following statistics are taken from the 2009 Annual Report of the German Childhood Cancer Registry and relate to the period 1999-2008 (Kaatsch and Spix 2009). For the 0-<15 age group, age-standardised incidence rates are based on the World Standard (devised by Segi) (1960) which is commonly used as the standard population in cancer epidemiology. For the purpose of comparison, the composition of the baseline population (children) is shown in Table 3.6:

Table 3.6: Composition of the Segi World Population (Segi 1960) for children under 15 years of age compared with the average German resident population 1999-2008 (Kaatsch and Spix 2009)

Age groups	World Standard Population based on Segi	German population 1999-2008	
Years	Weighting	Average absolute	Relative
0	0,08	718 140	0,06
1-<5	0,31	3 002 352	0,25
5-<10	0,32	4 004 880	0,33
10-<15	0,29	4 398 240	0,36
Total	1,00	12 123 612	1,00

Leukaemias and related diseases (ICCC-3 I, see above) are the most common type of malignancies in children and adolescents (<15 years) in Germany, comprising around 34 % of cases (Figure 3.1). An average of 1 820 new cases of cancer (based on ICCC-3) in the under-15s were registered each year during the period 1999-2008, with leukaemias and related diseases accounting for 620 of these cases on average. Of these cases of leukaemia, lymphoid leukaemia (ICCC-3 I(a)) is the single most common diagnosis overall, accounting for an annual average of 486 cases (78 %); acute myeloid leukaemia (ICCC-3 I(b)) is the second most common type of leukaemia, with an average of 84 cases (14 %) per year. LL has a distinct peak incidence between the ages of 2 and 4 years (Figure 3.2). AML is most common among children under the age of 2 (Figure 3.3). In 1999-2008, ALL accounted for 26.7 % of all cancers diagnosed in children under the age of 15. AML accounted for 4.6 %.

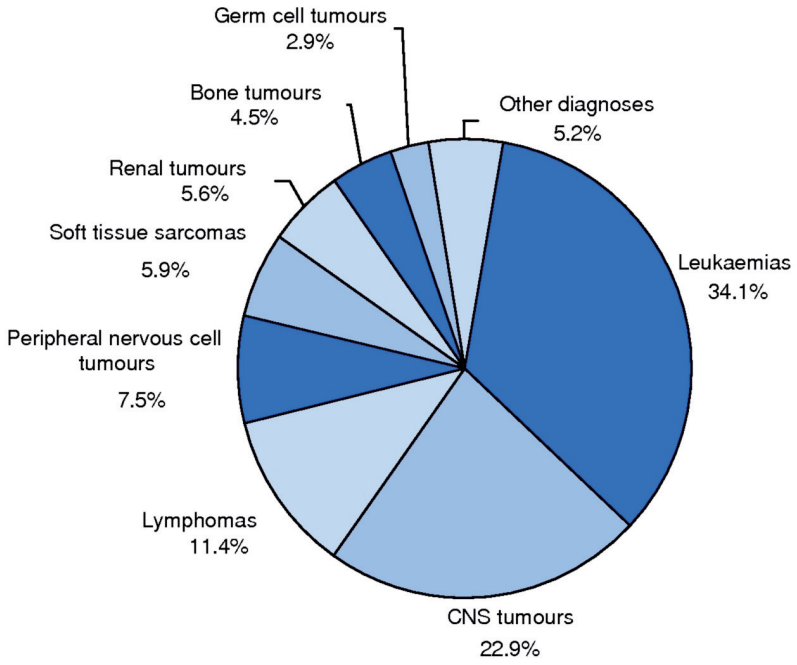

Figure 3.1: Relative frequencies of malignancies in children and adolescents (<15 years) in Germany in the most common diagnostic groups (determined for the period 1999 – 2008), German Childhood Cancer Registry (Kaatsch and Spix 2009); 100 %: all diseases defined in ICCC-3

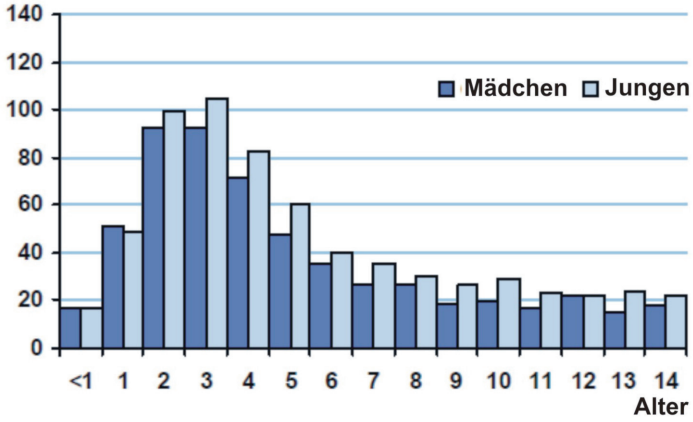

Figure 3.2: Age- and sex-specific annual incidence rates per million for lymphoid leukaemia (ICCC-3 I(a)) (determined for the period 1999 – 2008) (Kaatsch and Spix 2009); incidence rate: average number of new cases per million per year (f/m) (dark blue shading: girls; light blue shading: boys) (age in years shown on the x axis)

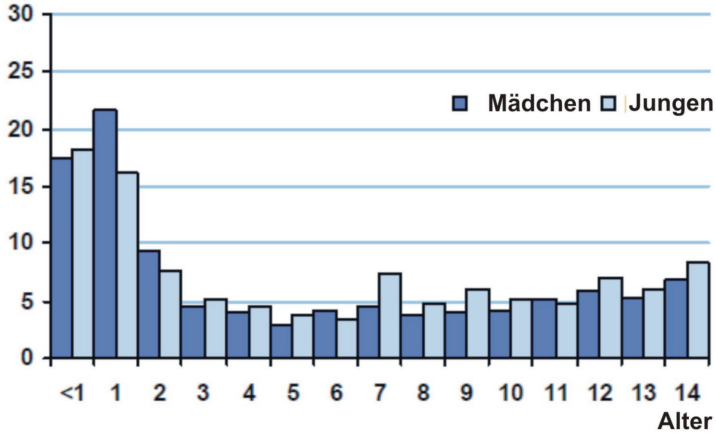

Figure 3.3: Age- and sex-specific annual incidence rates per million for acute myeloid leukaemia (ICCC-3 I(b)) (determined for the period 1999 – 2008) (Kaatsch and Spix 2009); incidence rate: average number of new cases per million per year (f/m) (dark blue shading: girls; light blue shading: boys) (age in years shown on the x axis)

Leukaemias and related diseases are rare amongst children and adolescents. The incidence rate for all childhood leukaemias in diagnostic group I according to ICCC-3 in Germany for the period 1999-2008 was 55 cases per million children per year (age-standardised). Besides the age-specific incidence rate and the mean incidence rate for ages 0-<15, the sum of the age-specific incidence rates, known as “cumulative incidence”, can also be defined. This can be expressed in simple terms as the probability

of a newborn child developing cancer before his or her 15th birthday. The mean cumulative risk for the under-15s is $7.9 \cdot 10^{-4}$. In other words, for every 1270 newborns, one case of childhood leukaemia is diagnosed before they reach 15 years of age. On average, boys develop the disease around 22 % more frequently than girls (Kaatsch and Spix 2009) (see Tables 3.7 and 3.8).

Survival for children with cancer, and especially leukaemia and related diseases, has markedly improved in recent years, with a good 80 % of all children and adolescents with leukaemia now surviving for at least 15 years (extrapolation based on data for the years 1999-2008 in (Brenner and Spix 2003)). The reason is that almost 100 % of cases are now treated in accordance with a constantly developing, centrally monitored protocol within the framework of diagnosis-specific treatment optimisation studies (TOPs) under the auspices of the Society for Paediatric Oncology and Haematology (*Gesellschaft für Pädiatrische Onkologie und Hämatologie – GPOH e.V.*). (see Section 2.3). The mortality rate (death rate) in Germany is around 11 deaths per million children per year. The mean cumulative risk of dying of leukaemia before the age of 15 is 1.6 · 10-4. This equates to one death per 6 250 children under 15 years of age (Kaatsch and Spix 2009).

Table 3.7: Overview of lymphoid leukaemia (ICCC-3 I(a)) in Germany, 1999-2008. Total number of all malignancies classified according to ICCC-3 in 1999-2008: 18 195 (Kaatsch and Spix 2009)

Relative % of all childhood malignancies	26,7 %
% of patients treated according to protocol	99,7 %

	Girls	Boys	Total
Number of cases	2 172	2 686	4 858
Standardised incidence rate[a] per million per year	40,3	46,6	43,6
Cumulative incidence per million (0-14)	569	665	618
Sex ratio (m/f)			1,2

Age-specific incidence rates per million per year				
	<1 year	1-<5 years	5-<10 years	10-<15 years
Number of cases	122	2 419	1 385	932
Incidence rate	17,0	80,6	34,6	21,2
Median age at diagnosis				4 years and 9 mon.

	5-year	10-year	15-year
Survival probabilities	90 %	87 %	86 %

[a] *Standard: Segi World Standard Population (Segi 1960)*

Incidence rate: average number of new cases per million per year

Age standardisation: weighted average of the age-specific rates using a standard population (Table 3.6)

Cumulative incidence: sum of the age-specific incidence rates per year

Table 3.8: Overview of acute myeloid leukaemia (AML) in Germany, 1999-2007. Total number of all malignancies classified according to ICCC-3 in 1999-2008: 18 195 (Kaatsch and Spix 2009)

Relative % of all childhood malignancies	4,6 %
% of patients treated according to protocol	98,0 %

	Girls	Boys	Total
Number of cases	397	442	839
Standardised incidence rate[a] per million per year	7,3	7,5	7,4
Cumulative incidence per million (0-14)	103	108	106
Sex ratio (m/f)			1,1

Age-specific incidence rates per million per year				
	<1 year	1-<5 years	5-<10 years	10-<15 years
Number of cases	128	271	181	259
Incidence rate	17,8	9,0	4,5	5,9
Median age at diagnosis				5 years and 9 mon.

	5-year	10-year	15-year
Survival probabilities	66 %	64 %	63 %

[a] *Standard: Segi World Standard Population (Segi 1960)*

Incidence rate: average number of new cases per million per year

Age standardisation: weighted average of the age-specific rates using a standard population (Table 3.6)

Cumulative incidence: sum of the age-specific incidence rates per year

Myelodysplastic syndrome (MDS, ICCC-3 I(d)) was not classified as malignant until the early 2000s, shortly after its systematic registration began. Other types of leukaemia, including the chronic myeloproliferative diseases, mainly occur in adults and are very rare in children (accounting for just 2 % of diagnostic group I according to ICCC-3) (Kaatsch and Spix 2009).

3.2.3 Temporal trends in Germany

In Germany, the impact of dramatic changes in social conditions on the occurrence of childhood leukaemia, among other things, could be observed after reunification. A recent detailed trend analysis of childhood malignancies in Germany therefore examined the incidence rates separately for western and eastern Germany (Spix et al. 2008a).

In western Germany, ALL incidence rates (ICCC I(a)) have increased fairly steadily, by 0.7 % annually (95 % CI: 0.2 %-12 %), since 1987. This is in agreement with the trend reported for the rest of Europe (see above) (Coebergh et al. 2006, Kaatsch et al. 2006, Steliarova-Foucher et al. 2005b).

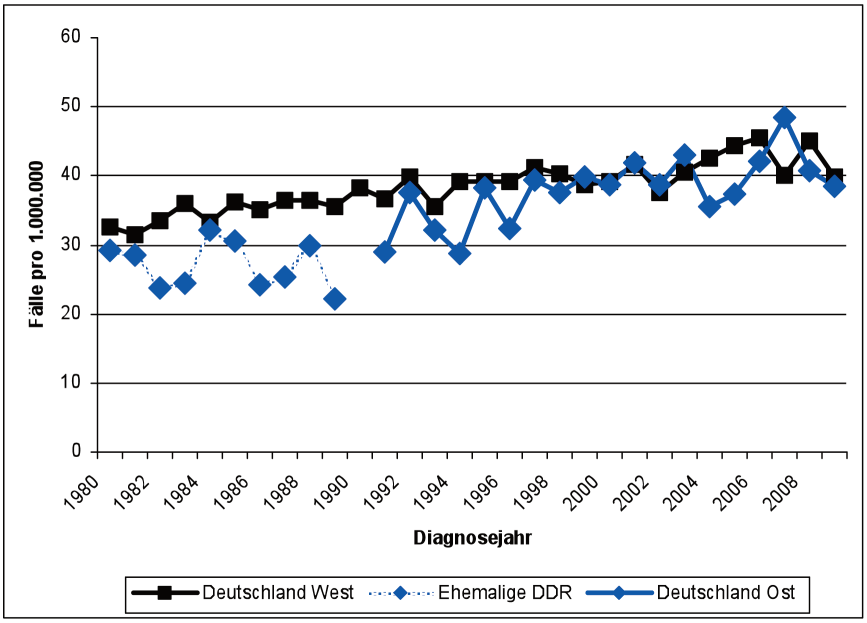

Figure *3.4: Age-standardised incidence rates of LL from 1980-2009 for the former German Democratic Republic (GDR) (ICCC I(a)), western Germany and eastern Germany (ICCC-3 I(a)). Source of GDR data: ACCIS. Source of data for Germany: German Childhood Cancer Registry. Age standardisation: Germany 1987*

Key:
Diagnosejahr = Year of diagnosis
Fälle pro 1.000.000 = Cases per million
Deutschland West = western Germany
Ehemalige DDR = former GDR
Deutschland Ost = eastern Germany

In the GDR, incidence rates were relatively constant at around 20 % below the western German level, which must be assumed to have been complete, given that reporting was mandatory and the GDR had a centralised health system. Incidence rates rose after reunification until 1998, reaching the western German level, and are now increasing slowly in line with the trend that can be observed in western Germany (Figure 3.4), with a statistically significant average increase of 2.1 % per year (95 % CI: 0.6 %-3.7 %) between 1989 and 1998. This is assumed to have been caused by changes in life style, in particular the substantial drop in birth rate (by around 50 %), less day care in infancy, less crowded homes, and more children without siblings. This agrees with the hypotheses presented by the authors of various studies (Kaatsch et al. 2006, Steliarova-Foucher et al. 2005b) for the similar upward trend observed

elsewhere in Europe. These factors are under discussion in individual studies as being potential risk factors for ALL, especially in early childhood (McNally et al. 2001, Eden 2010, Gilham et al. 2005, Stiller 2004) (see Section 6.3).

For AML, a much smaller and non-significant trend could be observed (0.3 % p.a., 95 % CI: -0.8 %-1.4 %). In view of the small number of cases, however, the trend would have to be very substantial in order to be discernable beyond normal statistical fluctuations (Spix et al. 2008a).

3.3 Spatial analysis of childhood leukaemia

3.3.1 General comments on "clusters" in (cancer) epidemiology

"Cluster" is a term often used in connection with rare diseases such as childhood leukaemia; in most cases, however, it is not clearly defined. The simple question "do clusters exist?" cannot be answered if presented in this form. It is essential to define, first of all, what is meant by a "cluster" in the individual case, and then determine whether there are any spatial units which meet the predefined criteria.

One (of several possible) working definitions of "cluster" is given as follows: "Aggregation of relatively uncommon events or diseases in space and/or time in amounts that are believed or perceived to be greater than could be expected by chance" (Last 2001).

Other terms used in this methodological environment are: disease mapping (often termed "atlas" in German), geographic epidemiology, and spatial statistics. What they all have in common is that they involve the analysis of data with spatial relevance.

The analysis of spatial data can focus on a variety of goals or questions, requiring different methodologies to be applied and leading to many different interpretations:

- Are there any spatial aggregations (see above)?
- Where are the spatial aggregations?
- Do any spatial aggregations exist in a predefined area, e.g. a country?
- Can the existence of a spatial cluster or clusters hypothesised by third parties be confirmed or refuted (small-scale survey)?
- Are there any spatial trends (obvious distinctions, specific urban/rural trends, coastal zones ...)?
- Is there stronger clustering than could reasonably have arisen through chance alone?

- Are there any spatial aggregations around predefined potential exposure sources?

- Are there any connections between a spatially distributed disease variable and one (or more) spatially distributed risk factor(s) which are the subject of study? (This question is customarily addressed within the parameters of environmental epidemiology.)

It must be emphasised that the tenor of questions such as “are there... ?” and “where are there ...?” directly conflicts with the general question “Is there stronger clustering than could reasonably have arisen through chance alone?” (Besag and Newell 1991). A single community or a small number of communities can deviate significantly from the overall mean without producing a greater than expected spread in the general analysis of all communities.

The methodology applied to the analysis will depend, firstly, on the questions posed and, secondly, on the type of available data, and, specifically, the degree of aggregation.

There is a general consensus that a distinction must be made between routine reporting, as required by cancer registries, and research which, as far as possible, is hypothesis-driven.

Routine reporting

For a cancer registry, continuity of presentation is important. As such reports are intended to be read by the non-specialist public as well, a simple style of presentation, as far as possible, is recommended here. Traditional depictions of spatial distribution (generally based on administrative units, e.g. with colouring based on percentiles) using conventional statistical models (incidence rates, SIR[a], p-value, or a combination of these) are often used in cancer registries and also in cancer mapping (Figure 3.5). This approach depicts, above all, the strong natural spread of the SIR or rates, which may be attributable to the typical properties of the underlying Poisson distribution but also to differences in population size in the administrative units. Smoothed maps are particularly suited to make large-scale structures (spatial trends, assuming that they exist) visible. They are less suitable, however, as a means of presenting small-scale spatial aggregations.

Homogeneity (taking account of population size) can be tested using one of the conventional models for testing homogeneity (based, for example, on Gail or Potthoff-Whittinghill (Muirhead 2006, Potthoff and Whittinghill 1966)). In statistics,

[a] Comparison of observed cases with expected cases based on total incidence.

homogeneity is understood as meaning that all spatial units are random samples from a distribution with one and the same underlying disease incidence rate; in other words, there are no systematic differences between them. A significant heterogeneity test acts, at least, as a warning sign in the interpretation of a map, but is not "proof" that a relevant cluster exists.

Conversely, some tests (such as the SaTScan test developed by Kulldorff and Nagarwalla (1995)) or similar procedures such as those presented by Alexander and Boyle in IARC Publication 135 (1996)) aim to detect clusters with the greatest possible sensitivity. Some authors (e.g. Rothmann, see (Schlattmann 1996)) have voiced criticism that such procedures can lead to artefacts or are oversensitive. These methods can be used as an alarm system, but they do not offer statistical proof that a cluster exists. They are therefore more suited for use in infectious disease epidemiology.

Research

Research should always seek to test specific statements of prediction ("hypotheses") and therefore entail the use of specific analytical procedures whose description is beyond the scope of this paper. In childhood leukaemia, for example, systematic efforts have been made to investigate clusters around specific predefined point sources (e.g. nuclear installations or broadcasting transmitters).

3.3.2 Spatial comparisons within Germany

A key characteristic of rare diseases such as childhood leukaemia is the clear geographical variation in incidence rates / mortality rates. It is usually difficult to determine whether these differences are statistical in nature or whether they are caused by regional variables (Figures 3.5a and 3.5b).

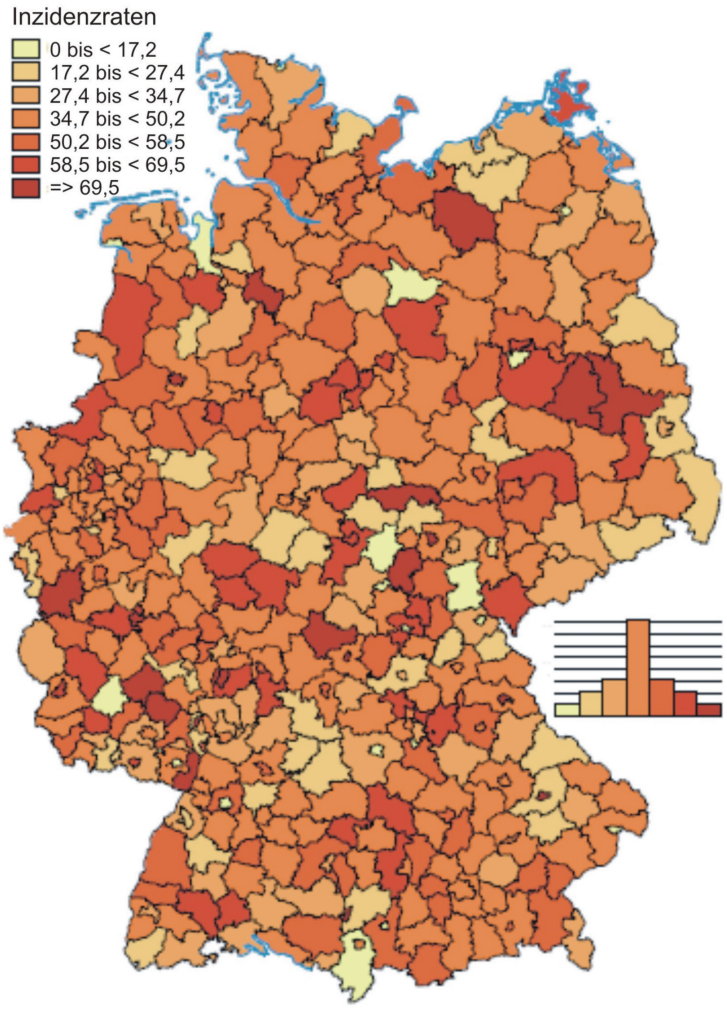

Fig. 3.5a: Annual standardised incidence rates per million by districts (Landkreise) (Germany 1999-2008) for lymphoid leukaemia (ICCC-3 I(a)) (Kaatsch and Spix 2009); relates to children under 15 years of age; histogram: number or percentage of districts (Landkreise) in the colour categories. Distribution was defined on the basis of percentages, i.e. 5 %, 10 %, 15 %, 40 %, 15 %, 10 % and 5 %, creating the borders between the colour codes. (Inzidenzraten = incidence rates; decimal points in figures are represented by a comma).

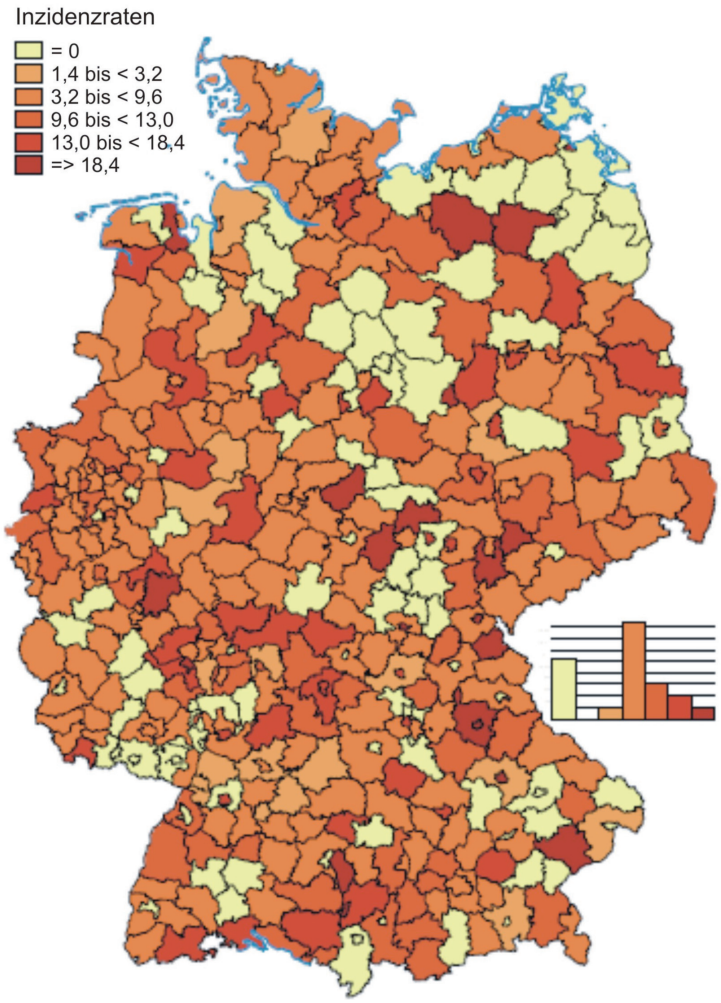

Fig. 3.5b: Annual standardised incidence rates per million by districts (Landkreise) (Germany 1999-2008) for acute myeloid leukaemia (ICCC-3 I(b)) (Kaatsch and Spix 2009)); relates to children under 15 years of age; histogram: number or percentage of districts (Landkreise) in the colour categories. Distribution was defined on the basis of percentages, i.e. 5 %, 10 %, 15 %, 40 %, 15 %, 10 % and 5 %, creating the borders between the colour codes. The second category is unoccupied, as no cases were observed in more than 15% of the districts. In districts with observed cases, the smallest incidence rate was 1.4 cases per million per year. (Inzidenzraten = incidence rates; decimal points in figures are represented by a comma).

The German data for the 1980s were analysed as part of a European study (see (Alexander et al. 1998) below). They were not analysed separately until 1995 and more recently in 2010. The 1995 analysis found no evidence of clustering in Germany (Westermeier and Michaelis 1995). The analyses by Westermeier and Michaelis were carried out at municipality, not district level. The recent analysis investigated possible spatial clustering and space-time clusters at the municipality level as well, using the Potthoff-Whittinghill model and SaTScan, but showed no evidence of a tendency to clustering (Schmiedel et al. 2010).

3.3.3 International studies on clusters of childhood leukaemia

An early European study from the 1980s, which analysed data from 17 countries (EUROCLUS), including Germany, showed a statistically significant trend to spatial clustering, although the trend was weak (Alexander et al. 1998). The clustering was most marked in areas with intermediate population density. There have been no further studies on this comprehensive scale since then.

To date, the spatial distribution of cases of childhood leukaemia has probably been studied most frequently and intensively in the United Kingdom, where complete registration over a great many years provides a very good dataset for this purpose. Some analyses of the British data with regard to clustering are discussed critically by Bithell (2001).

A recent review of the British data (COMARE 2006, McNally et al. 2009) describes the existence of (small-scale) spatial and space-time clustering for ALL, especially in children aged 1-<5 years, but not for AML. For ALL, the clustering trend also had a time component. As argued in earlier studies by the same research group, an infectious component is discussed in this context as a possible cause (Birch et al. 2000). Muirhead (2006) undertook a theoretical analysis of the methodology used in this study and concluded that the Potthoff-Whittinghill test offers an acceptable power to detect general heterogeneity (i.e. the existence of clusters), at least when heterogeneity is relatively clear or the expected case numbers are not too small.

In this context, it must be borne in mind that in the United Kingdom, these studies can be conducted at the level of "wards", i.e. very small spatial units which are relatively socioeconomically homogeneous with an average population of around 5 000. By comparison, German municipalities and districts, US counties or French *communes* are far larger entities. The detectability of very small-scale processes naturally decreases with a higher degree of aggregation. As a specific characteristic of Germany, it should be mentioned that due to merging of administrative units in recent decades, the average size of municipalities/districts has increased substantially, with a corresponding decrease in the number of spatial units. The individual German federal states continue to have specific features of their own as well.

A recent study conducted in France detected a weak trend towards clustering of acute leukaemias for part of the 1990s, the period under review, again only for 0- to 4-year-old children (Bellec et al. 2006).

A Swedish population-based study, which utilised fairly sensitive test procedures and analysed national data for the period 1973-1993, found no evidence of the presence of geographical clusters (Hjalmars et al. 1996). A further study using similar data and matched controls observed some excesses relating to date and place of birth, but found no statistically significant clustering around time of diagnosis (Gustafsson and Carstensen 2000). The authors conclude that this observation is in support of the hypothesis that pre- or perinatal infections can induce a process leading to leukaemia.

A case-control study by Dockerty et al. in New Zealand also found no evidence of clustering (1999a).

A Greek study used the Potthoff-Whittinghill method and concluded that there was more heterogeneity in urban than in semi-urban areas (Petridou et al. 1997), with evidence for spatial clustering. The possibility cannot be excluded that lifestyle differences, such as those observed on a large scale in the European regions (e.g. eastern/western Europe, see Section 3.2.1.2), may come into play here, albeit on a smaller scale.

A more methodological study in Ohio (USA) found no consistent evidence of significant overall clustering for leukaemia for the under-15s for the period 1996-2003 (Wheeler 2007). The data were geocoded to the street level. However, the sensitive instruments additionally used, such as the SaTScan test mentioned above, and alternative methods produced conflicting results.

Laurier et al. (2008) applied a series of more qualitative criteria and concluded that out of 198 nuclear sites investigated, only three local excesses can be considered confirmed childhood leukaemia clusters. These are the clusters near the Sellafield plant and the Dounreay plant in the UK and near the Krümmel plant in Germany (see Section 5.1). These researchers did not investigate possible clusters unrelated to nuclear sites. A recent study in Germany (Schmiedel et al. 2010), however, suggests that the relatively high incidence rates observed in the municipalities around Krümmel still lie within the range of normal variability and are not unusual.

Based on this evidence, the question whether childhood leukaemias (and particularly LL) show a tendency to space-time clustering can be answered as follows: “probably not, but if so, then weakly and on a very small scale”.

4 Epidemiological Studies on Ionising Radiation and Childhood Leukaemia

Exposure to ionising radiation is an established risk factor for childhood leukaemia. A wealth of literature, published in the fields of epidemiology and radiation biology, is available as a basis for assessing the risk of developing or dying from leukaemia following exposure to ionising radiation. Risk estimates provide information about the number of excess leukaemia cases that can be expected in a given population (e.g. children and adolescents) that is exposed to radiation. It is not possible to predict which individuals will develop the disease or die, nor the time of onset or death. Indeed, the occurrence of leukaemia cannot, as yet, be precisely attributed to previous exposure to radiation, as no specific features of radiation-induced leukaemia have been identified.

There are many different scenarios in which exposure to ionising radiation can occur which may be associated with childhood leukaemia. They include pre- and post-natal diagnostic procedures and the therapeutic use of ionising radiation. Parental occupational and other exposure must also be considered, as must exposure to natural radiation. This chapter reviews the available studies which have investigated these various scenarios.

4.1 Epidemiological measures and terminology

Various key terms used in epidemiology are defined below.

Case	A person identified as having the disease, disorder or condition under investigation.
Control	A person without the disease, disorder or condition under investigation.
Bias	Deviation caused by a systematic error in data collection. Bias cannot be corrected during the evaluation of the study.
Confounder	The association between a risk factor (e.g. radiation) and the disease can be explained in full or in part by another factor, the confounder. The problem can be addressed in the analysis of studies if data on the confounder are collected.
Power	Statistical power of a study; corresponds with the probability that for defined significance level α, an actually increased (or decreased) risk can be identified as such.

Confidence interval (CI)	The CI gives a measure of statistical precision or uncertainty. The 95% CI is often used. The true rate will be inside the 95% confidence interval on 95% of occasions.
Prevalence	The proportion of persons with a particular disease or risk factor within a given population at a given time.
Incidence	Measures of incidence describe the probability of a new occurrence of the disease (or other event) within a defined time period.
Incidence rate	Number of new cases occurring during the observation period divided by the sum of the periods in which the study participants were observed and were free from the disease which is the subject of the study. Takes into account that possibly, not all study participants were observed throughout the entire study period. Often expressed as cases per 100 000 person-years; in childhood cancer epidemiology, often expressed as cases per million person-years.
Mortality rate	A measure of the number of deaths from the disease of interest during the observation period, calculated by dividing the number of deaths by the sum of the periods in which study participants were observed. Takes into account that possibly, not all study participants were observed throughout the entire study period. Often expressed as cases per 100 000 person-years; in childhood cancer epidemiology, often expressed as cases per million person-years.
Relative risk (RR) Odds ratio (OR)	The ratio of the incidence rate from the disease of interest in an exposed population to that in an unexposed population; if RR = 1, there is no difference in risk between the two groups. Measure of relative risk, determined in case-control studies. The OR is not based on incidence data.
Excess relative risk (ERR)	Additional incidence rate (mortality rate) in an exposed population, divided by the incidence rate (mortality rate) in the non-exposed population. Numerically, excess relative risk is expressed as relative risk (RR) minus one (ERR = RR – 1).

Risk coefficient	Increase of risk per unit exposure or per unit dose. In the simplest hypothetical case, namely a population which has all received the same dose and an unexposed population, the risk coefficient is the quotient of the ERR and the dose received by the exposed persons.
Cluster	A (cancer) cluster is defined as a greater than expected number of (cancer) cases within a group of people, a geographic area, or a period of time.

4.2 Survivors of the atomic bombings of Hiroshima and Nagasaki

The studies of the Japanese survivors of the atomic bombings of Hiroshima and Nagasaki (Life Span Study, LSS) provide little information about leukaemia risk after in utero irradiation. In the cohort of more than 1 000 Japanese children who were in utero at the time of the atomic bomb explosions, two children developed solid cancers, but there was not one case of leukaemia. The absence of any leukaemia cases is a significantly different result compared with what would be expected based on the OSCC findings (Doll and Wakeford 1997). As, however, follow-up of survivors of the atomic bombings did not begin until more than five years after exposure, the dataset does not include any cases of cancer in children under 5 years of age and is therefore of little use for estimating leukaemia risks after *in utero* irradiation.

4.3 Medical radiation exposure of affected children

In relation to the induction of leukaemias due to medical radiation exposure, a distinction must be made between various scenarios:

- *in utero* (pre-natal) exposure to radiation from diagnostic procedures performed on the mother during pregnancy

- post-natal exposure from diagnostic procedures

- post-natal exposure during therapeutic interventions.

4.3.1 Pre-natal exposure

Table 4.1 provides an overview of selected studies which investigated the relative risk of developing leukaemia after *in utero* (pre-natal) exposure to radiation from diagnostic procedures performed on the mother during pregnancy. The most comprehensive analyses date back to the 1950s and 1960s (Bithell and Stewart 1975, Monson and MacMahon 1984); it should therefore be borne in mind that radiation doses administered during diagnostic procedures were much higher at that time than those used later.

Table 4.1: Relative risks (with 95 % confidence intervals) for "at least one x-ray examination" in selected studies of childhood leukaemia and cancer following in utero exposure to X-rays (SSK 2009

Study	Reference	Endpoints(s)	Relative risk (RR)
OSCC (1953-1967)[a]	Bithell and Stewart (1975)	Leukaemia and lymphoma mortality	1,47 (1,32-1,64)
OSCC (1953-1967)[a]	Bithell and Stewart (1975)	Mortality from lymphoid leukaemias	1,54 (1,34-1,78)
NE US maternity hospitals (1947-1960)[b]	Monson and MacMahon (1984)	Leukaemia mortality	1,52 (1,18-1,95)
Swedish study (1973-1989)	Naumburg et al. (2001)	Leukaemia incidence	1,11 (0,87-1,47)
US study (1989-1993)[b]	Shu et al. (2002)	ALL[c]-incidence	1,2 (0,83-1,7)
UKCCS (1992-1996)[a]	Roman et al. (2005)	Leukaemia incidence	1,1 (0,8-1,7)
Meta-analysis of 31 studies, excluding OSCC	Wakeford (2008)	Leukaemia	1,26 (1,14-1,39)
Meta-analysis of 13 studies, excluding OSCC	Bithell (1993)	Leukaemia and, predominantly, cancer mortality	1,37 (1,22-1,53)
Meta-analysis of 6 cohort studies	Doll and Wakeford (1997)	Cancer and, predominantly, leukaemia	1,2 (0,7-2,0)

[a] *Time period of cancer incidence*

[b] *Time period of births*

[c] *ALL = acute lymphoblastic leukaemia*

OSCC: Oxford Survey of Childhood Cancers

UKCCS: United Kingdom Childhood Cancer Study

The Oxford Survey of Childhood Cancers (OSCC) is the largest study available. Bithell and Stewart (1975) analysed data for children younger than 16, and for the period 1953-1967, including a total of 4 771 cases of leukaemia / lymphoma mortalities. A total of 661 of the cases (13.8 %) and 483 of the controls (10.1 %) had in utero exposures resulting from X-ray examinations of their mothers. This produced an (unadjusted) relative risk of 1.49 (95 % CI: 1.33-1.67).

Monson and MacMahon (1984) conducted a study of leukaemia mortality during the first 10 years of life in a sample of 14 276 children born in 1947-1960, with 597 cases of leukaemia. 9.4 % of the children in the sample, and 13.4 % of the children who had died of leukaemia, had been exposed prenatally to diagnostic X-rays. After adjustment for birth order (see Section 6.3), this produced a relative risk of 1.52 (95 % CI: 1.18-1.95).

A Swedish population-based study (Naumburg et al. 2001) found that X-ray examinations carried out during pre-natal care were not associated with a significant overall increased risk for childhood leukaemia (OR = 1.11, 95% CI: 0.83-1.47). The researchers found little evidence of a dose response.

A case-control study in the US found no evidence that *in utero* diagnostic X-ray examinations performed on the pelvis of the mother were linked with an increased risk of childhood ALL (Shu et al. 2002); 3.0 % of the mothers of ALL cases and 2.6 % of mothers of controls reported that they had undergone X-ray examinations during pregnancy. The relative risk was 1.2 (95 % CI: 0.8-1.7).

Roman et al. (2005) reported findings from the United Kingdom Childhood Cancer Study (UKCCS). Out of the 1 196 leukaemia cases registered in 1992-1996, 48 (4 %) had been exposed to X-rays *in utero*, compared with 3.8 % of the 4 759 controls. The study found no association between radiation exposure and leukaemia. The relative risk for all leukaemias was 1.1 (95 % CI: 0.8-1.5).

A meta-analysis of 31 studies (excluding the OSCC) (see above) on the association between the risk of childhood leukaemia and *in utero* exposure to diagnostic X-rays (Wakeford 2008) produced a relative risk of 1.26 (95 % CI: 1.14-1.39).

4.3.2 Post-natal exposure

4.3.2.1 Diagnostic procedures

With regard to indications, external radiation exposure during diagnostic procedures differs hardly at all in children and adults. Due to the small size of the patient and hence the involvement of other tissues and larger organ volumes, however, the effective dose for children is increased. The use of specialised examination protocols enables the dose to be reduced.

When performing diagnostic nuclear medicine procedures on children (e.g. thyroid, kidney, oncological diagnostics), a body weight-adapted dose of radionuclides is administered. The paediatric use of open radionuclides is governed by various Guidelines issued by the German Society of Nuclear Medicine (*Deutsche Gesellschaft für Nuklearmedizin*).

Various studies have investigated a possible association between the risk of childhood leukaemia and exposure to radiation from diagnostic procedures performed during the early years of life. Table 4.2 summarises the findings of some of these studies.

Table 4.2: Relative risks (with 95 % confidence intervals) as shown in selected studies which investigate childhood leukaemia and cancer following postnatal X-ray examinations (SSK 2009 with amendments)

Study	Reference	Endpoint(s)	Relative risk
US study (1989-1993)[a]	Shu et al. (2002)	ALL incidence, 0- to <15-year-olds	1,1 (0,9-1,2)
US study (1989-1993)[a]	Shu et al. (2002)	ALL-incidence, 0- to <6-year-olds	1,0 (0,8-1,3)
German study (1980-1994)[b]	Meinert et al. (1999)	Leukaemia incidence, 0- to <15-year-olds	0,78 (0,65-0,93)
Canadian study (1973-1998)[b]	Infante-Rivard (2003)	Leukaemia incidence[c]	1,48 (1,11-1,97)[d]
Meta-analysis of 8 studies, excluding Shu et al. (2002)	Wakeford (2008)	Leukaemia	0,98 (0,89-1,08)
German study (1976-2003)	Hammer et al. (2009)	Leukaemia incidence between 1980 and 2006	1,08 (0,74-1,52) - SIR -
German study (1980-1994)[b]	Meinert et al. (1999)	Cases of acute leukaemia	0,78 (0,65-0,93)[e]

a *Time period of births*
b *Time period of cancer incidence*
c *0- to 9-year-olds in the period 1980-1993, 0- to 14-year-olds in the period 1994-1998*
d *Relative risk for two or more X-ray examinations*
e *OR for 1-4 X-ray examinations, OR for 4 or more examinations (only 39 cases); OR= 1*

The largest study to date was conducted by Shu et al. (2002). This case-control study included 1 811 children (without trisomy 21) diagnosed with ALL between 1989 and 1993 under the age of 15 years and a similar number of matched controls. A minimum latency period of two years between the X-ray examination and the ALL diagnosis was assumed. Children under one year of age were excluded from the study. Overall, the study found no association between childhood ALL and post-natal diagnostic X-ray exposures (OR: 1.1; 95 % CI: 0.9-1.2). For ALL in the 0-<6 age group, an OR of 1.0 was produced (95 % CI: 0.8-1.3)[a].

Meinert et al. (1999) investigated 1 184 acute leukaemia cases in children under the age of 15 years during the period 1980-1994 and around twice as many controls. Cases were identified from the German Childhood Cancer Registry; for leukaemia, completeness of registration is around 95 %. X-ray examinations during the year preceding diagnosis – or if cancer was diagnosed during the first year of life, during the six months preceding diagnosis – were not considered. For children who had undergone 1 to 4 X-ray examinations, a negative association between exposure and leukaemia was found (OR 0.78; 95 % CI: 0.65-0.93). No increased risk was found for individuals who had undergone a larger number of X-ray examinations (OR 1.00; 95 % CI: 0.65-1.55).

A Canadian case-control study investigated childhood acute lymphoblastic leukaemia diagnosed between 1980-1993 (phase 1: age <10 years) or 1994-1998 (phase 2: age <15 years) (Infante-Rivard 2003). The study included 701 cases and the same number of controls. 24.9 % of cases and 18.8 % of controls had undergone two or more X-ray examinations (excluding dental) during the first years of life. Very few cases (0.5 %) and controls (0.3 %) had been exposed *in utero*. The odds ratio was 1.48 (95 % confidence interval: 1.11-1.97), adjusted for age of mother and type of schooling. An increase in leukaemia risk with number of post-natal X-ray examinations was identified as a significant trend. The increase in risk following a single post-natal exposure to X-rays was found to be insignificant.

A major weakness affecting all three studies discussed above is that the exposure data are based on information provided by the mothers, not on clinical records. Recall bias[b] therefore cannot be ruled out.

Wakeford (2008) conducted a meta-analysis of eight studies on childhood leukaemia risk following medical diagnostic exposure to ionising radiation after birth, excluding the study by Shu et al. (2002). This produced a relative risk of 0.98 (95 % CI: 0.89-

[a] The original publication refers to 1-<6-year-olds, not 0-<6-year-olds, as infants under 1 year old were excluded from the study. Furthermore, this latency period additionally excludes children <2 years of age, so this should actually read 2-<6.

[b] Error due to inaccuracy or incompleteness of a survey respondent's recall of past events when answering a question in a subsequent survey; refers particularly to differences in recall between cases and controls.

1.08). In a more recent study (Hammer et al. 2009, 2010), the risk of childhood cancer was studied in a cohort of 92 957 children who had been examined with diagnostic X-rays during 1976-2003. Radiation doses were reconstructed as precisely as possible and conversion coefficients developed specifically for the medical devices and standards used at the radiology department. Individual cumulative effective dose varied between 1.08 μSv and 343 mSv; the median radiation dose was 7 μSv. Newly diagnosed cancers occurring between 1980 and 2006 were determined through record linkage to the German Childhood Cancer Registry. 33 leukaemia and 13 lymphoma cases were found in the cohort. No increase in leukaemia risk with diagnostic radiation was observed. Nor was disease frequency higher compared with the rest of the child population (SIR 1.08; 95 % CI: 0.74-1.52).

4.3.2.2 Therapeutic radiation exposure in childhood

The use of therapeutic nuclear medicine (radioiodine treatment) to treat thyroid diseases in children is governed by Guidelines issued by the German Society for Radiation Oncology (*Deutsche Gesellschaft für Radioonkologie – DEGRO*). Firm data on leukaemia incidence in children and young people following nuclear medicine treatment are not available.

A review of paediatric radiooncology, i.e. irradiation of malignant diseases in childhood, can be found in Kortmann et al. (2009). In Germany and Austria, the use of radiation therapy to treat childhood cancers generally takes place in accordance with studies by the Society for Paediatric Oncology and Haematology (*Gesellschaft für Pädiatrische Onkologie und Hämatologie – GPOH e.V.*). Recommendations on radiotherapy are generally a matter for discussion by the Paediatric Radiation Oncology Working Group (APRO) of the GPOH and the German Society for Radiation Oncology (DEGRO). Patients with primary disease have a much better prognosis than those in relapse. For that reason, initial treatment is generally based on very aggressive multimodal protocols. Combined with good recovery rates, this leads to a high level of early and, above all, chronic side-effects. For infants and young children, an age-adapted recommendation on radiotherapy is made. The paediatric doses can vary and amount to as much as 60 Sv.

Multimodal treatment, mainly with polychemotherapy, and the possibility of a genetic predisposition to other cancers mean that estimating the risk of secondary leukaemia occurring after therapeutic irradiation is problematical. In the majority of cases, the secondary leukaemia is AML.

Allard et al. (2010) analysed a case-control study in order to estimate the risk of leukaemia and myelodysplastic syndrome as a function of radiation dose, taking into account heterogeneous radiation dose distribution, after treatment for a solid tumour in childhood. It included 61 patients with leukaemia matched with 196 controls. Wha-

tever the model, the researchers failed to evidence a role for the radiation dose in the risk of later leukaemia, when adjusting for epipodophyllotoxin and anthracycline doses. This also applied when restricting the analysis to ALL.

External radiation therapy is also used to treat *benign diseases*, primarily hemangioma. In a Swedish cohort study of 14 624 infants exposed to ionising radiation for skin hemangioma from 1920 to 1959, all of whom were less than 18 months old at the time of first exposure (Lundell and Holm 1996), there were 11 deaths from acute childhood leukaemia. There were no significant associations between childhood leukaemia and bone marrow dose.

In a comparative analysis of radiation-associated leukaemia in Japanese A-bomb survivors exposed in early childhood and *in utero* and medically exposed groups, Little (2008) concludes that relative risks tend to be lower for medically exposed persons than the Japanese A-bomb survivors.

4.4 Natural radiation exposure in childhood

A number of epidemiological studies, with various methodologies and designs, have been conducted around the world to investigate a possible association between childhood leukaemia and exposure to natural radiation, particularly radon in the home (Alexander et al. 1990, Henshaw et al. 1990, Muirhead et al. 1991, Richardson et al. 1995, Thorne et al. 1996, Evrard et al. 2005, Lubin et al. 1998, Kaletsch et al. 1999, UKCCS 2002a, UKCCS 2002b, Henshaw 2002, Steinbuch et al. 1999, Raaschou-Nielsen et al. 2008). A number of the ecological studies have reported positive associations (Henshaw et al. 1990, Muirhead et al. 1991, Richardson et al. 1995, Thorne et al. 1996, Evrard et al. 2005, Henshaw 2002), whereas the available case-control studies were unable to confirm an association (Lubin et al. 1998, Kaletsch et al. 1999, Steinbuch et al. 1999) or even reported a negative association (UKCCS 2002a, UKCCS 2002b). The ecological studies have been widely criticised and their findings are considered by some authors to be unreliable (Alexander et al. 1990, Kaletsch et al. 1999, SSK 1999, SSK 2002, WHO 2009).

Currently, there are just three larger case-control studies which serve as a basis for drawing conclusions about a possible association between childhood leukaemia and exposure to radon (Lubin et al. 1998, UKCCS 2002a, Raaschou-Nielsen et al. 2008). Two of them (Lubin et al. 1998, UKCCS 2002a) found no evidence for an association between radon exposure and childhood leukaemia. More recently, a Danish study (Raaschou-Nielsen et al. 2008) suggests a positive association between ALL and estimated exposure to radon in residences of children (i.e. a positive dose-response). This case-control study included 2 400 incident cases of leukaemia, central nervous system tumour, and malignant lymphoma diagnosed in children between 1968 and 1994 in the Danish Cancer Registry. The reported findings are based on 1 153 cases of leukaemia (including 860 ALL cases) and their matched controls. A linear dose-response analysis showed a

56 % increase in the rate of ALL per 1 kBq/m^3-years increase in exposure (cumulative exposure). The association with ALL persisted in sensitivity analyses and after adjustment for potential confounders. No association was found with the other types of childhood cancer. However, a weakness of the study is its methodology: radon concentration of cases and controls was estimated using a model instead of being determined by direct measurements. This method of determining exposure does not satisfy the criteria that should be applied to radon studies; measurements are the only way of reliably determining radon concentration in a home, as actual radon levels can vary considerably and are strongly dependent on the characteristics of individual homes.

In other case-control studies, the number of cases is too small or difference in exposure levels (exposed/unexposed) is too low for the studies to be informative (Kaletsch et al. 1999, Schüz et al. 2003).

In Germany, a population-based case-control study in Lower Saxony investigated a reported association between elevated indoor radon concentrations and childhood cancer, with special regard to leukaemia. However, it was based on a small number of cases (82 cases of leukaemia and 209 matched controls), and overall mean indoor radon concentrations were low compared with the measured levels in other studies. A number of ecological studies on general regional distribution patterns of childhood leukaemia were also published (Kaatsch et al. 1995, Breckow et al. 1995).

Numerous ecological studies on radon exposure in childhood have been conducted. There is considerable scope for confounding in these studies (Alexander et al. 1990, Kaletsch et al. 1999, SSK 1999, SSK 2002, WHO 2009). Their conclusions are therefore likely to be misleading, so they should not be taken as evidence that radon is a cause of these diseases. A French study conducted in 2006 generated considerable interest (Evrard et al. 2006a); this was based on an ecological study design (geographical correlation study) and investigated regional associations between childhood leukaemia incidence and natural background radiation. In its assessment, however, SSK (SSK, 2007) does not give weight to the findings of this study, mainly due to the general weaknesses associated with its ecological study design.

4.5 Parents' exposure to radiation

4.5.1 Parents' occupational exposure – the Gardner hypothesis

It has often been hypothesised that parents' occupational exposure to radiation may be associated with diseases in their offspring. Parental preconceptional irradiation is under discussion as a possible cause.

In 1984, excesses of childhood leukaemia were reported in the area around Sellafield nuclear plant in the West Cumbria district of the United Kingdom (Black 1984). Du-

ring the period 1955-1983, 7 cases were observed in young people under 25 years of age living in nearby Seascale. Five of these 7 cases occurred among the under-10s; the expected statistical value for this age group was 0.5.

In 1990 and 1991, Gardner at al. published the results of a case-control study of leukaemia, non-Hodgkin's lymphoma and Hodgkin's disease among 97 children, adolescents and young adults from West Cumbria. Various potential risk factors were investigated, including the possible effect of the father's occupation.

Relative risk for leukaemia was lower for children of fathers employed by the coal mining industry. Relative risk was higher for children of fathers employed in agriculture, the iron and steel industry, the chemical industry and also of fathers employed at the Sellafield plant receiving a recorded external dose of 100 mSv or more prior to the child's conception, or a personal dose of more than 10 mSv received in the six months immediately preceding the child's conception. For these children, the relative risk was 6.4 (95 % CI: 1.57-26.3).

The authors hypothesise that irradiation causes mutations in the father's germ cells which are passed on to the child and manifest as an increased number of leukaemia cases ("Gardner hypothesis"). This hypothesis is controversial and has supporters and opponents (McKinney et al. 1991, Roman et al. 1993, Shu et al. 1994, Meinert et al. 1999, Watson 1991, Urquhart et al. 1991, Kinlen 1993, McLaughlin et al. 1993, Doll et al.1994, Shu 2002).

First, Neel and Schull (1991) and Doll et al. (1994) have pointed out that no excess leukaemia was noted in the rest of Cumbria where > 90 %(!) of the births to Sellafield employees occurred (Draper et al. 1993). Second, data on the children of male atomic bomb survivors have not shown an increased incidence of leukaemia (Yoshimoto et al. 1990), despite these fathers receiving a significantly greater mean dose of radiation than the children's fathers at Sellafield.

The role of parental occupational exposure has also been investigated among uranium miners who worked for the Wismut company. An initial evaluation of data for a feasibility study for a BfS cohort study (Kreuzer et al. 2009) revealed a number of methodological problems which would greatly limit the informative value of such a study, notably a lack of information about the cause of death of deceased offspring in a large percentage of cases, especially for years of death 1950-1970, a considerable number of unidentified offspring, and relatively low gonad doses prior to conception.

There is still no scientific evidence for the "Gardner hypothesis".

4.5.2 Other studies on parental exposure to radiation

When considering the role of parents' exposure to *natural* radiation, it must be borne in mind that in most cases, offspring are exposed as well. Parental exposure is therefore indistinguishable from child's exposure. The latter is discussed in Section 4.2. No studies have been published on the effect of parental exposure to radiation during diagnostic or therapeutic procedures.

Data on parental exposure to radiation during military operations are available for the survivors of the atomic bombings in Japan and for exposure to radioactive fallout from atmospheric nuclear weapons testing. Childhood leukaemia incidence in Hiroshima between 1998 and 2000 did not differ significantly from general incidence in Japan (Sugiyama et al. 2009). A recent meta-analysis found no evidence of a wave of excess cases of childhood leukaemia following exposure to radioactive fallout from atmospheric nuclear weapons testing (Wakeford et al. 2010).

4.6 Radiation sensitivity in children and adolescents

It is important to note that radiation sensitivity cannot be quantified with one specific figure. The question of radiation sensitivity must always be answered in relation to a specific endpoint. When inducing apoptosis, high radiation sensitivity may be beneficial with regard to cancer risk, as this higher apoptotic propensity may reduce the number of surviving tumour cells. The endpoint considered in this chapter is leukaemia, first and foremost, and the following remarks about radiation sensitivity in children and adolescents therefore relate solely to leukaemia.

The measure used as a basis for comparison is important. Often, the excess relative risk (ERR) model is used for cancers. This can be problematical, however, especially if the spontaneous frequency of the observed cancer is very low. A small number of excess cases can then affect ERR very strongly. In this scenario, it is important to consider that excess cumulative absolute risk EAR_K may be a more appropriate model.

It must also be borne in mind that it is not possible to talk about "**the**" child – or indeed "**the**" adult – for such an entity does not exist. This statement not only applies to differences in individual radiation sensitivity; rather, it reflects the fact that in adults, it makes a difference whether a 20-year-old or a 50-year-old is used as the basis for comparison, and similarly, age is a factor which must also be considered when studying children and adolescents (Preston et al. 2007). It is also important to consider possible sex-specific differences in radiation sensitivity and the fact that women may be more sensitive to radiation, potentially affecting their cancer risk. At present, however, there are not enough data available to draw firm conclusions (SSK 2010).

A specific feature of the results relating to *in utero* exposure to radiation is that it is particularly difficult to determine doses accurately. Most *in utero* exposures to radiation occurred in the 1940s and 1950s during diagnostic procedures using X-rays. Efforts to determine dose retrospectively are beset by uncertainties (Wakeford and Little 2003). However, accurate dosage data are needed in order to quantify the risks associated with radiation exposure.

A major concern is that in many of the epidemiological studies in which questionnaire data are used to determine past exposure *in utero* or in childhood, inaccuracy of recall ("recall bias") or selection ("selection bias") may distort results (Wakeford 2008).

Nonetheless, it is generally accepted that a foetus/embryo or very young child is more sensitive to radiation exposure than a mature adult. There are three main reasons for this:

1. Foetal and juvenile tissues display much higher rates of cell proliferation than adult tissue.

2. A factor of particular relevance to leukaemia is that in early post-natal life (i. e. in infants and young children), the bones – especially peripheral bones – contain more active red bone marrow than adult bones, increasing the risk of leukaemia. As a consequence, under identical conditions, exposure will deliver significantly greater radiation doses – around 25 % to 30 % higher – to the bone marrow of infants than to adults (Petoussi et al. 1991).

3. When considering the whole-life risk after radiation exposure in childhood, it must be borne in mind that lifespan also plays a role: if initiated in childhood, a cancer has a much longer timeframe in which to become clinically manifest. This is an important factor as a rule, but is obviously not relevant here, as this paper focuses solely on childhood leukaemias.

For the reasons stated above, however, it is difficult to quantify the precise extent of this higher radiation sensitivity. If an attempt is made at quantification, the criteria used for the comparison must be stated very clearly.

Wakeford concludes that for childhood leukaemia after *in utero* exposure, the absolute risk is in the order of 3% per Gy (2008), corresponding to an approximately threefold increased risk compared with adults. He estimates the ERR to be in the order of 50 per Gy.

Based on analysis of the Hiroshima/Nagasaki data, Richardson et al. (2009) calculate an excess relative risk (ERR) of around 70 per 1 Gy for 10-year-olds ten years after the atomic bombings. This extremely high ERR then decreases sharply with increasing time since exposure, reaching around 1 after 30 years. For 20-year-olds, the ERR ten years after exposure is around 15 per 1 Gy, and for 30-year-olds and over, it is around 2 per 1 Gy. It makes little sense to conduct analyses of *in utero* exposure using the Hiroshima and Nagasaki data, as systematic registration of leukaemia cases did not begin until 1950; the main period of risk for leukaemia after *in utero* exposure, i.e. the first five years, is therefore undocumented.

The problems associated with expressing differences in radiation sensitivity in terms of an ERR or EAR are apparent from the Hiroshima and Nagasaki data. In 1994, Preston et al. conducted similar analyses, but unlike Richardson et al. (2009), these were based on an EAR, not an ERR model. Based on an EAR model, the risk for 10-year-olds is approximately double that of 25-year-olds and older, based on data five years after exposure, and is virtually identical at 10 years and more after exposure.

Another option for estimating radiation sensitivity is to utilise the finding of Preston et al. (2007) that for every 10 age-years, radiation sensitivity (expressed in terms of excess relative risk for solid cancers) decreases by around 17 percentage points. This would mean that the risk for a foetus/very young child is around twice as high compared with a 60-year-old adult. For adolescents, the figure is likely to be somewhat, but not substantially, lower.

Further information about the risks after *in utero* exposure and exposure in childhood can be obtained from the scientific annex to the SSK's Assessment of the KiKK Study (SSK 2009).

4.7 Quantitative estimation of leukaemia risk following exposure to ionising radiation

In relation to the increased risk of contracting leukaemia in childhood following exposure to ionising radiation, three types of exposure are considered relevant: preconception parental exposure, in utero (pre-natal) exposure, and exposure early in life. Results of studies on risk following preconception radiation exposure are controversial and, according to current knowledge, are unsuitable as a basis for estimating risk (SSK 2009; see also Section 4.5). Risk estimates are therefore discussed solely in relation to in utero (pre-natal) exposure and exposure during the first years of life.

As is generally the case when estimating radiation-induced cancer risk, evidence of increased risk following exposure in the low dose range is particularly significant for childhood leukaemia as well. Various studies have investigated childhood leukaemia risk after in utero irradiation. In the UNSCEAR 2000 Report and the updated report

published in 2006, this is discussed and evaluated in detail. Particular weight is given here to the findings of the Oxford Survey of Childhood Cancer (OSCC), which comprises a number of case-control studies of childhood cancer and considers the effects of in utero radiation exposure during X-ray examinations of mothers in the 1950s and 1960s. Uterine doses were in the order of 10 mGy. The UNSCEAR 2006 Report largely bases its discussion of the OSCC on a review by Wakeford and Little in 2003. No explicit estimates of risk coefficients are provided for leukaemia, but only for all childhood cancers. However, there is no evidence that the relative risks for leukaemia differ significantly from the risk for all childhood cancers after in utero exposure.

Overall, UNSCEAR 2006 concludes that there is evidence that exposure to the relatively high doses applied during X-ray examinations in the 1950s and 1960s increased the risk of childhood cancer. UNSCEAR cites the excess relative risk (ERR) as being around 0.5 (a figure which the original literature states is probably too high) for all types of cancer and leukaemia in the under-15s following *in utero* exposure to a mean dose of 10 mGy. In a more recent review from 2008, Wakeford explicitly states this value as applying to leukaemia as well, but emphasises again that this is probably an overestimation. UNSCEAR draws attention to the great uncertainty surrounding risk estimates due to the absence of precise dosage data. Various analyses of the OSCC data refer to values ranging from 0.13 to 0.51 following *in utero* exposure to a mean dose of 10 mGy (Table 4.3). In its Assessment of the KiKK Study, the SSK gives an ERR of 0.4 for leukaemia risk in the under-5s following in utero exposure to a mean dose of 10 mGy.

In Section 3.2.2, it was stated that the leukaemia incidence in the under-15s is 7.9 cases for every 10 000 newborns. An ERR of 0.4 per *in utero* dose of 10 mGy thus produces an absolute risk coefficient of 0.03 % per 10 mGy; in other words, for every 10 000 newborns who receive an *in utero* dose of 10 mGy, an additional three cases of leukaemia can be expected before they reach their 15th birthday. In his study, Wakeford (2008) also states an absolute risk coefficient of 0.03 % per 10 mGy, but emphasises the considerable uncertainties, with the stated value likely to be an overestimation.

The studies of the Japanese survivors of the atomic bombings of Hiroshima and Nagasaki (Life Span Study, LSS) provide little information about radiation-induced childhood leukaemia after *in utero* irradiation. In the cohort of more than 1 000 Japanese children who were *in utero* at the time of the atomic bomb explosions, two children developed solid cancers, but there was not one case of leukaemia. The absence of any leukaemia cases is a significantly different result compared with what would be expected based on the OSCC findings (Doll and Wakeford 1997). As, however, follow-up of survivors of the atomic bombings did not begin until more than five years after exposure, the dataset does not include any cases of cancer in children under 5 years of age and is therefore of little use for estimating leukaemia risks after *in utero* irradiation.

In a recent analysis using multi-model inference (Walsh and Kaiser 2011), nine recently published leukaemia risk models, developed with the Japanese A-bomb epidemiological mortality data, were included in a model-averaging procedure so that the main conclusions do not depend on just one type of model or statistical test. Relatively high estimated values for ERR were obtained for childhood leukaemia, but were not found to be statistically significant due to the small number of cases. The estimated risk for adolescence is lower than for childhood, but statistical significance is increased due to the larger number of cases. The ERR in adolescence is relatively independent of age at exposure. Following exposure at 7 years of age to a bone marrow dose of 1 000 mSv, the observed excess relative leukaemia mortality risk at age 17 is 18, with a 95 % confidence interval of 0.6 to 36. Due to the non-linear dose/response relationship, the estimated values for ERR per unit dose are decreased at lower doses. For exposure at age 7 to a bone marrow dose of 100 mSv, the estimated value of the excess relative leukaemia mortality risk is 0.9. This value for the lower doses is not significant due to the small number of cases in the LSS.

The relative risks reported in the OSCC are generally consistent with a number of other case-control studies on childhood cancer and leukaemia risk following *in utero* X-ray examinations. The available cohort studies, particularly the LSS studies mentioned above, report lower risks. Due to the very small number of cases, however, the cohort studies are not particularly informative.

Childhood cancer after pre-natal exposure to radiation is discussed in ICRP Publication 60 (1990). These studies are also discussed by the ICRP in its Publication 103 (2007). It emphasises the uncertainties and inconsistencies in the various studies but, like UNSCEAR, assumes that there is sufficient evidence for an increased risk following *in utero* exposure. ICRP 60 and 103 do not give any explicit risk estimates for childhood leukaemia, but merely state that the childhood leukaemia risk is around 3 times higher than in adulthood and that pre-natal exposure entails approximately the same excess risk as post-natal exposure in early childhood.

The SSK undertook a detailed assessment of the various studies in a statement in 2008 (SSK 2009). Overall, it concludes that the estimated ERR for leukaemia in the under-5s after pre-natal exposure with low-LET radiation is around 0.4 for 10 mGy.

The body of data available for estimating risk after post-natal exposure is smaller than that available for *in utero* exposure. Here too, the majority of studies focus on exposure to X-rays. Overall, it would seem that there is a lower risk of childhood leukaemia from X-ray examinations conducted post-natally than *in utero* (SSK 2009). UNSCEAR (2006) and ICRP 103 (2007) conclude that relative risk decreases with increasing age. The BEIR VII Report (2006) provides data for estimating relative and absolute childhood leukaemia risk based on dose. According to the report, the excess relative mortality risk coefficient per unit dose at age 15 following exposure at age 10 is 20 Gy^{-1},

while the excess absolute risk (EAR) per unit dose is around 4 cases per 10^4 person-years per Gy. Assuming that exposure occurs at age 2 and the stated value of the EAR per dose applies with a minimum latency period of 2 years (mean) for age range 4-14 years, this produces an absolute risk coefficient of 0.4 % Gy^{-1} for this period.

Overall, risk estimates for childhood leukaemia after exposure to radiation *in utero* or in childhood are beset with uncertainties. If it is assumed that *in utero* exposure to a dose of 10 mGy gives rise to a excess relative risk of 0.4 for leukaemia, this means that in the under-15s, in addition to the 7.9 spontaneous cases of childhood leukaemia per 10 000 newborns, an additional three cases (approximately) can be expected as a result of this exposure. The doubling dose is then 25 mGy. For exposure during early childhood, the excess relative risks are within the same order of magnitude, but there is a trend towards rather lower values. Due to the shorter time period, compared with *in utero* exposure, in which leukaemia could still occur in childhood or adolescence, the excess absolute risks are correspondingly smaller.

Table 4.3: Excess relative risk for cancer before the age of 15 years following in utero exposure to 10 mGy based on analyses of the OSCC data (based on SSK 2009). In the OSCC, the relative risks were similar for cancer and leukaemia.

Period of mortality data	Reference for relative risk	Reference for dosimetry	ERR after *in utero* dose of 10 mGy[a]	Reference for risk coefficient
1953-1972[b]	Bithell and Stiller (1988)	UNSCEAR (1972)	0,29 (0,17; 0,44)	Bithell and Stiller (1988)
1953-1978[c]	Bithell (1993)	Mole (1990b)	0,51 (0,28; 0,76)[d]	Doll and Wakeford (1997)
1958-1961	Mole (1990b)	Mole (1990b)	0,38 (0,0 7; 0,79)	Doll and Wakeford (1997)
1953-1972[b]	Bithell and Stiller (1988)	Mole (1990a)	0,13[e]	Wakeford and Little (2003)

[a] *Best estimate and 95 % CI*
[b] *Limited to birth cohort 1943-1972*
[c] *Limited to birth cohort 1940-1976*
[d] *This figure is described by the authors themselves and also in subsequent publications (Wakeford and Little 2003, Wakeford 2008) as probably too high*
[e] *No CI stated*

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5 Epidemiological Studies on Leukaemia in Children and Adolescents in the Vicinity of Nuclear Facilities

5.1 Studies outside Germany

Since the 1960s, various studies conducted in the USA, the United Kingdom and other countries have investigated whether proximity to nuclear facilities is associated with an increased risk of childhood leukaemias/lymphoma or infant mortality. A detailed review of the studies published to 1999 was presented by Grosche (1999). It shows that incidence is slightly higher among children and adolescents in the immediate vicinity of the nuclear installations; this is most apparent among the youngest age groups (0-4 years old or 0-9 years old, depending on the study). Based on calculations of exposure rates, a causal link is regarded as implausible. It is also noteworthy that the deviations from expected values occurring near existing sites were also found in the vicinity of potential sites (Cook-Mozaffari et al. 1989, Keller et al. 1992, Kaletsch et al. 1997, Bithell et al. 1994, Grosche 2006).

Studies conducted outside Germany since 2000 have focused mainly on the United Kingdom and France[a]. A detailed discussion of these studies is contained in the reports on the KiKK Study (SSK 2008b, SSK 2009). They can be summarised as follows:

- The tenth COMARE report (COMARE 2005) examined the incidence of cancers in children under the age of 15 years in the vicinity of the major nuclear installations in England, Wales and Scotland during 1969-1993, and concluded that there was no significant evidence of excess numbers of cases of childhood leukaemia and non-Hodgkin's lymphoma in any 25 km area local to the nuclear installations. No trend with distance was found. However, an increased risk of childhood leukaemia was observed around the reprocessing plants.

- A new analysis of data gathered near British nuclear power plants was designed to match the German KiKK Study as far as possible (see below) (Bithell et al. 2008). The study is based on data from the National Registry of Children's Tumours (NRCT) relating to cases of acute leukaemia registered in the under-5s between 1969 and 2004. The study investigated whether there was a trend of increasing incidence of leukaemia in electoral wards and the nearness of a ward to the nuclear installation. It was found that the incidence rate in the study area corresponded to the average rate in the UK. No association between incidence rate and proximity to the nuclear installations was found.

[a] The COMARE 11th Report and the Swiss CANUPIS Study were not published until after this Scientific Reasoning was finalised and therefore could not be considered in the present volume.

- After a previous study in France has suggested an increased incidence rate of leukaemia from 1978 to 1992 in people aged 0 to 24 years and living in the vicinity of the La Hague nuclear waste reprocessing plant (Pobel and Viel 1997), an expanded survey for the years 1978-1998 was conducted which described the occurrence of different leukaemia types (Guizard et al. 2001). The study used three zones defined according to their distance from the site (0 to 10 km; 10 to 20 km; and 20 to 35 km). The observed number of cases of leukaemia in the study region as a whole was consistent with the expected value. The study found an increased incidence of leukaemia in the 0-10 km zone. The highest incidence was observed in the 5 to 9 years age group (SIR=6.38; 95% CI: 1.32, 18.65), mainly consisting of acute lymphoblastic leukaemia cases. The authors recommended that further investigations of these findings should be carried out.

- As a consequence of these observations, the Groupe Radioécologie Nord-Cotentin (Nord-Cotentin Radioecology Group) was set up in 1997 and tasked with making a retrospective estimation of the local population's exposure levels to ionising radiation, particularly in the vicinity of the La Hague reprocessing plant. In the Summary Report of its work to 2000, the Group concludes that based on the dose estimates, the total number of leukaemia cases in persons under 25 years of age which can be assigned to routine releases from local nuclear facilities during the period 1978-1996 is around 0.002 – many orders of magnitude less than the four cases observed during this period (NCRG 2008).

- The ecological study by Boutou et al. (2002) investigated a possible association between population mixing and the occurrence of leukaemia in young people (less than 25 years) around the nuclear installations at La Hague resulting from the influx of workers. Between the years 1978 and 1992, this area experienced a major influx of workers for the construction of the plant. Urban communes were considered as the reference population. Significantly, the incidence rate ratio was 2.7 in rural communes belonging to the highest tertile of population mixing. The risk became stronger for acute lymphoblastic leukaemia in children 1-6 years old in the highest tertile of population mixing (IRR=5.5). The authors conclude that these findings provide further support for a possible infective basis of childhood leukaemia (see also Section 6.3.).

- Evrard et al. (2006b) investigated the incidence of childhood leukaemia around French nuclear installations based on estimated bone marrow doses due to gaseous radioactive discharges. The study area (40 km^2) centred on a total of 24 French nuclear installations. Doses to the red bone marrow were estimated using radionuclide discharge data and local weather data. The estimated doses (arithmetic mean) in the communes located in the vicinity of the nuclear installations were calculated. The observed number of cases of childhood leukaemia within the study area was lower than the national average but the difference was not

statistically significant. There was no evidence of a trend in standardised incidence ratio (SIR) with any of the age groups studied, including the under-5s.

- In a new analysis of data for the area around French nuclear power plants, the evaluation sought to emulate, as far as possible, the conditions of the KiKK Study (Laurier et al. 2008b). The analysis is based on the expanded data in (Evrard et al. 2006b) from (White-Koning et al. 2004) for 1990-1998. The study considered all cases of leukaemia aged less than 5 years while resident in communes within the vicinity of nuclear sites. There were 5 observed cases, compared with 5.2 expected cases (SIR = 0.96; 95% CI: 0.31-2.24). The results indicated no decreasing trend of risk with increasing distance from the NPPs.

- In early 2008, the IRSN in France undertook a review of epidemiological studies published in the international literature describing the frequency of leukaemia in children and young adults close to nuclear facilities in various countries around the world (IRSN 2008, Laurier et al. 2008a). The review analysed descriptive results from 198 nuclear sites in 10 different countries, including multi-site studies (25 studies in 8 different countries). IRSN concludes that worldwide, three local excesses met the stated evaluation criteria and can be considered confirmed childhood leukaemia clusters. These are the clusters near the Sellafield plant and the Dounreay plant in the UK and near the Krümmel plant in Germany. No excesses were reported for the majority of plants. At some sites, the excesses were not confirmed, or possible clusters were identified. Several studies also investigated other possible causes unrelated to radioactivity and radiation, but could not explain the observed clusters.

- In 2007, Baker and Hoel (2007) published a meta-analysis of rates of childhood leukaemia in proximity to nuclear facilities. It is discussed in detail in (SSK 2008b, SSK 2009). A total of 136 sites were used. Effects models were calculated separately for age group 0-10 years and for age group 0-25 and for the distances <16 km and 0-25 km. All the models produced elevated risks in the range +2 % to +25 % and in most cases were statistically significant. In the view of the authors, no publication bias existed. However, the authors also found no evidence to support a hypothesis that could explain the excess risk. The methodology used by Baker and Hoel (2007) in their meta-analysis has been criticised by some authors, however, mainly on the grounds that the criteria for the selection and inclusion of studies are not always clear and that sites with zero observed cases appear to have been systematically underrepresented (Spix and Blettner 2009).

5.2 Studies on leukaemia in the vicinity of North German nuclear power plants

In the period 1982 to 2001, 14 cases of childhood leukaemia (<15 years of age) were ascertained in the immediate vicinity of the Krümmel nuclear power plant and the GKSS Research Centre in Elbmarsch municipality and in Geesthacht. There were 12 cases of acute lymphoblastic leukaemia and two cases of acute myeloid leukaemia.

Various expert commissions were established to investigate the causes of this noticeable excess. A comprehensive review and evaluation of the findings can be found in the joint final report by the spokespersons of the commissions set up by the federal state of Lower Saxony (Wichmann and Greiser 2004). The existence of a cluster is undisputed. According to calculations by the German Childhood Cancer Registry for the periods 1985-2001, 1990-2001 and 1994-2003, the increase in the standardised incidence ratios (observed excess of cases in Elbmarsch municipality and in the 5 km radius around the nuclear installations at Geesthacht) is statistically significant.

In a case-control study on childhood leukaemia in Lower Saxony, Kaletsch et al. (1995) investigated whether there was evidence of an association between (specified) physical and chemical factors and childhood leukaemia and explored potential risk factors which might explain the observed clusters in Lower Saxony. The following conclusions, *inter alia*, were drawn from this study (Wichmann and Greiser 2004):

- Greaves' hypothesis that childhood leukaemia may be linked to poor development of the immune system in early childhood is supported by the following results: in children with leukaemia, vaccinations were less frequent, and the children possibly had fewer contacts with other children in infancy.

- Children who were X-rayed more than four times show a positive association with occurrence of leukaemia.

- Children who were born prematurely and had received intensive care treatment show a positive association with occurrence of leukaemia compared with the control group.

A multitude of factors potentially associated with the excess of leukaemia cases in the Elbmarsch were investigated. Researchers attempted to determine whether there were any other leukaemia clusters along the Elbe, and measured levels of pollution in the air, in drinking water, in the waters of the River Elbe, in soil and in milk from cows grazing in the area around the dikes. They investigated whether any specific local factors existed, such as contamination with ionising radiation (reactors, Chernobyl), electromagnetic fields (broadcasting facilities, high voltage power lines), industrial chemicals, contamination from earlier industrial use, or contamination at

children's playgrounds. The possible existence of risk factors in the home environment was also investigated, e.g. indoor air pollution from radon or solvents, specific factors relating to domestic cultivation of vegetables (pesticide/fertiliser use, rainwater) and use of pesticides/rodenticides. Biological and medical risk factors and markers were also investigated, such as antibodies to leukaemogenic viruses, chromosomal aberrations, exposure to ionising radiation during diagnostic procedures, and the use of medicines with potentially leukaemogenic side-effects. The results of all of these studies were negative.

The spokespersons of the commission set up by the federal state of Lower Saxony therefore drew the following conclusion (Wichmann and Greiser 2004):

"Reviewing all the results from all the studies, it must be concluded that ... there is no compelling evidence to support the hypothesis that there is a causal association between the excess of leukaemia cases among children living in the 5 km radius around the Geesthacht nuclear installations and the discharges from these installations in normal operation. ... Nor was there any evidence of any nuclear accident having occurred during the period under review and resulting in a massive discharge of radiation. In view of the scope of the studies already conducted ... there is at present no indication that continuing the investigations is likely to be successful."

In addition, the North German Leukaemia and Lymphoma Study found no indication that adults could be affected by emissions from nuclear power plants; it did, however, identify a link to insecticides and wood preservatives (*Norddeutsche Leukämie- und Lymphomstudie* [Northern German Leukaemia and Lymphoma Study], Hoffmann et al. 2003).

5.3 The KiKK Study

The Epidemiological Study on Childhood Cancer in the Vicinity of Nuclear Power Plants (KiKK Study) was a case-control study set up to investigate whether there is any correlation between residential distance to a nuclear power plant and the risk of contracting cancer by the age of 5 (Part 1 of the Study). In Part 2, a subgroup of cases and controls from Part 1 was questioned about potential risk factors which might act as confounders. The findings of the KiKK Study were published in several detailed reports (Spix et al. 2008b, Kaatsch 2008a, Kaatsch 2008b) and were additionally evaluated by the SSK. The SSK reports (SSK 2008b, SSK 2009) also examine other authors' analyses in considerable detail. Against this background, it is considered sufficient to confine the following discussion to the main findings of the KiKK Study.

5.3.1 Execution of the KiKK Study

In Part 1 of the KiKK Study, the study regions corresponding to the 16 nuclear power plants included in the study were defined in terms of the rural district (*Landkreis*) in which the relevant nuclear power plant is located, the nearest neighbouring rural district and the nearest rural district to the east. The study periods began, in each case, one year after a reactor was commissioned at the pertinent location and ended, in each case, five years after the last reactor at the location was decommissioned.

The cases consisted of all new tumours reported in the German Childhood Cancer Registry (GCCR) in Mainz in 1980-2003 for the study regions (place of residence at the time of diagnosis), and classified as malignant pursuant to the International Classification of Childhood Cancer (ICCC) (see Chapter 3). For every case, three sex- and age-matched controls were selected who lived in the same relevant nuclear power plant region when they were of the ages at which the cases were diagnosed.

The data for matched cases and controls were evaluated both continuously and categorially (exposure measure: 1/distance). In categorial evaluation, the data for the matched cases and controls were evaluated based on the categories of "residences at a distance of up to 5 km" and "residences at a distance of more than 5 km". Analogous evaluation was carried out for categories with a distance boundary of 10 km.

Part 2 of the KiKK Study was to take account of possible risk factors that could function as confounders. Overall, control families were less cooperative compared with case families; above all, recruitment was much less successful in the immediate vicinity of the nuclear power plants than more distant regions, and this effect was more noticeable among controls. This meant that distortion-free evaluation of Part 2 in accordance with the study plan could not be guaranteed. The following presentation and discussion of results therefore focus solely on Part 1 of the study.

5.3.2 Results of the KiKK Study

The main analysis of 1 592 cases of cancer and 4 735 control persons found a significant result for the coefficient of the inverse distance from residential address, at the time of the cancer diagnosis, and the nearest nuclear power plant. Within a 5 km radius around the nuclear power plants, the cancer risk for children younger than five was increased significantly, by a factor of 1.61, by comparison to the risk for the study area outside the 5 km radius.

For leukaemias (593 cases, 1 766 controls), a larger distance coefficient was found than was found for all cancer cases. Within a 5 km radius around the nuclear power plants, the leukaemia risk for children younger than 5 was significantly increased by a factor of 2.19 by comparison to the risk for the study area outside the 5 km radius. No statistical correlation was found between the risk of contracting CNS tumours and embryonic tumours and the distance to the nearest nuclear power plant.

The results of the categorial and continuous analyses were largely compatible, although due to the specified form of the correlation, the continuous analysis may well have led to an underestimation of the effect in the inner radius, with some overestimation outside this radius. This effect can be observed for both types of acute leukaemia.

Table 5.1: Estimated parameters from the conditional logistic regression model with continuous exposure (1/distance in km) for leukaemia and subtypes (under 5 years of age) (Kaatsch et al. 2008a)

Diagnostic group	β	Lower 95 %-CL	Cases (N)	Controls (N)
All leukaemias	1,75	0,65	593	1 766
Acute lymphoid leukaemias	1,63	0,39	512	1 523
Acute non-lymphocytic leukaemias	1,99	-0,41	75	225

β *regression coefficient; 95 %-CL, one-sided 95 % confidence limit*

The categorial effect for leukaemias was generally limited to the 5 km radius zones around the nuclear power plants.

No statistical correlation was found between the risk of contracting CNS tumours and embryonic tumours and the distance to the nearest nuclear power plant.

Table 5.2: Estimated odds ratios (OR) with lower limit of one-sided 95 % confidence interval (CI) and numbers of cases and controls by distance from nearest nuclear power plant[a] (Kaatsch et al. 2008b)

Zone	Categorical OR	Lower limit of 95% CI	Cases n	Controls n
< 5 km	2,27	0,80	37	54
5 to < 10 km	1,09	0,40	58	173
10 to < 30 km	1,01	0,38	332	1 048
30 to < 50 km	1,11	0,41	135	387
50 to < 70 km	0,90	0,32	27	92
≥ 70 km[b]	1,00	-	4	12

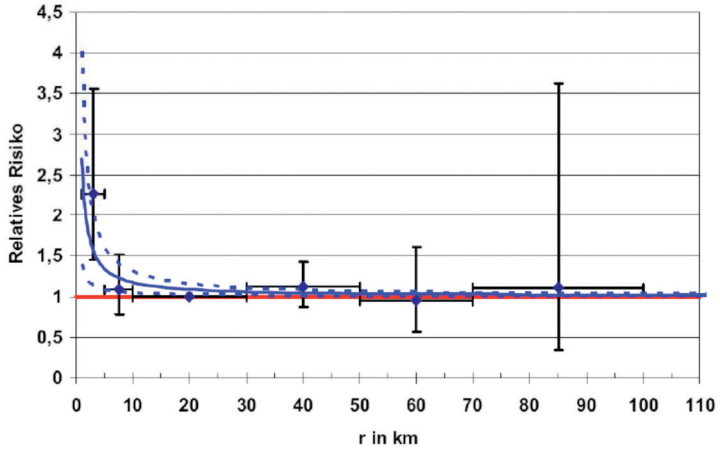
[a] *Leukaemias in children under 5 years, according to (Steliarova-Foucher et al. 2005a)*
[b] *Reference category*

A number of sensitivity analyses were carried out, which point to lower distance coefficients than those obtained in the main analysis.

The results of earlier ecological studies and a new ecological analysis (Kaatsch et al. 2008b) are compatible with the findings of the KiKK Study.

At the request of the German Commission on Radiological Protection (*Strahlenschutzkommission* – SSK), British epidemiologists Sarah Darby and Simon Read carried out an independent analysis of the raw data of the KiKK Study in 2008. Their analyses confirmed the KiKK Study's main conclusions and provided a number of additional findings (Darby and Read 2009).

Figure 5.1: Result of categorial evaluation (points) and continuous evaluation (lines) carried out by Sarah Darby and Simon Read (2008) for acute leukaemias in children younger than 5. The bounded straight lines along the x axis show the breadth of the relevant regions, while the bounded straight lines along the y axis show the 95% confidence intervals of the odds ratios. The unbroken line corresponds to an RR(x)= 1+ RR(x)= 1+βx model with x = 1/r and β = 1.7; the broken lines correspond to the β values for the limits of the two-sided 95% confidence interval; β = 0.39 and β = 3.02 [y-axis = relative risk] (Darby and Read 2009, Publication Series Reports of the Commission on Radiological Protection, Issue 58)



The most interesting additional finding was that the leukaemia risk was significantly higher in rural areas than in urban regions. The odds ratio (OR) was 2.54 (95 % CI: 1.62-3.97). This finding is independent of the increased risk within the 5 km radius zones.

The authors of the report on the comparative calculations conclude that there is an increased risk for childhood acute leukaemia within the 5 km radius zones around the nuclear power plants. The relevant causes are unknown.

Summary of the Assessment of the KiKK Study by the SSK

The results of the deliberations of the Commission on Radiological Protection (*Strahlenschutzkommission* – SSK) can be summarised as follows:

- The KiKK Study's new data confirm the results of earlier exploratory studies that found an increased risk of leukaemia, for children younger than five, within a 5 km radius around German nuclear power plants, relative to the risk in the outer areas around the relevant study areas. Studies carried out in other countries

produced conflicting findings, however. It thus cannot be concluded with finality that there is any evidence for increased rates of leukaemia, in general, in the vicinity of nuclear power plants.

- By virtue of its design, the KiKK Study exhibits numerous methodological weaknesses with regard to determination of exposure and surveying of influencing factors. Consequently, the study should not have been carried out in the manner in which it was carried out. In spite of such weaknesses, the study's design is suitable for the task of analysing dependence on distance.

- The evidence for increased cancer rates in children is limited to areas that are no more than 5 km from the relevant nuclear power plant sites. There is thus no justification for using attributable risks to calculate hypothetical additional cancer cases for greater distances.

- The study is thus not suited to the task of establishing a correlation with exposure to radiation from nuclear power plants. All of the radioecological and risk-based circumstances reviewed by the SSK indicate that exposure to ionising radiation caused by nuclear power plants cannot explain the result found by the KiKK Study. The additional radiation exposure caused by nuclear power plants is lower, by a factor of considerably more than 1 000, than the radiation exposure that could cause the risks reported by the KiKK Study.

- The natural radiation exposure within the study area, and its fluctuations, are both greater, by several orders of magnitude, than the additional radiation exposure caused by the relevant nuclear power plants. If one assumes that the low radiation exposures caused by the nuclear power plants are responsible for the increased leukaemia risk for children, then, in light of current knowledge, one must calculate that leukaemias due to natural radiation exposure would be more common, by several orders of magnitude, than they are actually observed to be in Germany and elsewhere.

- The KiKK Study was unable to survey risk factors to a sufficient degree. For this reason, the KiKK Study cannot be used to help explain the causal reasons for the observed distance dependence of leukaemia rates.

- The reason for the increased leukaemia rate that the KiKK Study observed in children is unclear. Since leukaemia is caused by multiple factors, numerous influencing factors could have been responsible for the observed result. If the many relevant conflicting findings in the literature, and the finding of the KiKK Study, are to be understood, more extensive, interdisciplinary research into the causes and mechanisms of the development of leukaemias in children will have to be carried out.

It should also be noted that in Issue 58 of its Publication Series, the SSK provides detailed information on all sources of human radiation exposure in Germany with special reference to the children of the KiKK Study. All sources of natural and man-made radioactivity and radiation are identified with their importance for external and internal radiation exposure. Each component of the highly variable natural radiation exposure is higher by some orders of magnitude than the reference person's exposures from both direct radiation or discharges of radioactive substances through airborne and liquid effluents at the most unfavourable exposure sites in the vicinity of NPPs in Germany.

C-14 is the predominant radionuclide of relevance to radiation exposure from airborne discharges of radioactive substances from nuclear power plants. Radiation exposure occurs through ingestion. Inhalation of C-14 does not contribute to a significant extent to exposure. Following the publication of the SSK's statement on the KiKK Study, other researchers (A. Körblein, *Kinderkrebs um Kernkraftwerke: Stationen einer Aufklärung*, umwelt•medizin•gesellschaft 24, 1/2011, 15 – 23) hypothesised that discharges of C-14 from NPPs are characterised by short-term peaks and not by a constant low dose rate, and that rather regularly, peak values are registered which might occur during periodic revision and refuelling. The resulting higher dose rates, it was argued, will therefore increase the risk of leukaemia. The SSK has examined this hypothesis and found that, taking account of the biokinetics of ingestion, the radiation exposure resulting from a constant low dose rate of C-14 is higher than that resulting from short-term peaks. The dose rates resulting from short-term peaks are only marginally higher than those resulting from the constant low dose rates and therefore cannot be considered as the cause of the increased leukaemia risk observed in the KiKK Study.

5.4 Meta-analysis commissioned by the Alliance 90/The Greens parliamentary group in the German Bundestag

After the publication of the SSK reports (SSK 2008b, SSK 2009), Greiser conducted a "meta-analysis and analysis" of leukaemia cases among children around nuclear power plants in Germany, the United Kingdom, France, Canada and the USA (Greiser 2009). Data on 80 NPPs and the leukaemia cases occurring in their vicinity were included in the analysis. The observed cases were compared with expected cases. The meta-analysis was based on published data and additional data from cancer registries in the USA. For all age groups studied, the incidence of leukaemia was reported to be significantly increased by 13-24 % in the vicinity of nuclear power plants, relative to the corresponding national average rate.

In an evaluation of this meta-analysis, the Institute of Medical Biostatistics, Epidemiology and Informatics (IMBEI) at the University of Mainz (Merzenich et al. 2009) criticises the fact that it is unclear from Greiser's report whether the literature review was complete or selective, and that the report did not include an accurate description

of the statistical methodology used, making it impossible to determine which statistical analysis had been carried out. What's more, the pooled estimates shown in Tables 4-9 of the meta-analysis are all mathematically flawed: the standard method for calculating the pooled estimate for the SIR produces different results. For example, in Table 8, the total number of observed cases is 345, i.e. lower than the number of expected cases (349.04), but its quotient 0.988 does not correspond with the stated value of 1.22. The same applies to all the tables presented.

In sum, this meta-analysis by Greiser does not provide any arguments against the KiKK Study and the SSK's assessment of the current state of scientific knowledge. The data available to the international scientific community about a possible association between living near a nuclear power plant and the risk of contracting leukaemia/lymphoma must still be classed as inconsistent, and there is still no convincing evidence that exposure to radiation from nuclear plants is responsible for the excesses observed in some cases.

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6 Other Risk Factors for Leukaemia

Many factors are suspected of triggering childhood leukaemia. These suspicions are mainly based on epidemiological studies. In most cases, however, these studies have produced highly inconsistent results. There are various reasons for this. Often, the conclusions are drawn from ecological studies, with all the problems that these entail (see Section 4.4). Many of the studies are based on populations that are too small. Furthermore, there are indications that leukaemia development is a multifactorial process (see Chapter 1); the contribution made by individual factors may be so small that it is almost impossible to prove epidemiologically. And finally, due to the small number of cases, the individual leukaemia subtypes are not considered separately in most studies: in the case of subtype-specific risk factors, the observed risks may be systematically underestimated.

As discussed in previous chapters, ionising radiation is well-documented as being a proven trigger or risk factor for leukaemias. This chapter discusses other risk factors which have been identified as possibly playing a role in leukaemogenesis, especially in children. Some of these factors are discussed in more detail in the scientific annex to the SSK's Assessment of the KiKK Study (2009).

6.1 Chemicals

As there is strong evidence that childhood leukaemia can originate *in utero* (see Section 6.6), a number of studies have investigated a possible association with exposure to chemicals before and during pregnancy. Here, some authors, at least, have reported increased risks associated with exposure to a wide range of chemicals, including maternal use of antihistamines or allergic remedies (Wen et al. 2002), hormones for infertility treatment (Shu et al. 2002), colorants to darken blond hair (Thompson et al. 2001), and exposure to benzene (Steensel-Moll et al. 1985). Paternal exposure to benzene prior to the child's conception has also been linked to an increased risk of leukaemia (Savitz and Chen 1990). Maternal consumption of alcohol during pregnancy was associated with an increased risk of childhood leukaemia (van Duijn et al. 1994), whereas smoking is reported as unlikely to contribute substantially to the risk of childhood leukaemia (Brondum et al. 1999).

Several recent meta-analyses have investigated an association between the risk of childhood leukaemia and exposure during pregnancy to residential pesticides. Bailey et al. (2010a) found some evidence of a modestly increased risk of ALL for professional pest control treatments done during the index pregnancy. Van Maele-Fabry et al. (2011) extracted RR estimates from 13 case-control studies on pesticide use published between 1987 and 2009. Statistically significant associations with childhood leukaemia were observed when combining all studies (mRR: 1.74, 95% CI: 1.37-2.21), with the strongest risk reported for exposure during pregnancy (mRR: 2.19, 95 % CI: 1.92-2.50). Similar

findings were reported by Turner et al. (2010) from a meta-analysis of 15 studies. Exposures during pregnancy to unspecified residential pesticides (summary OR = 1.54; 95 % CI, 1.13–2.11; I2= 66 %), insecticides (OR = 2.05; 95 % CI, 1.80–2.32; I2 = 0 %), and herbicides (OR = 1.61; 95 % CI, 1.20–2.16; I2 = 0 %) were positively associated with childhood leukaemia. However, all the authors warn that due to the limited data available, no firm conclusions could be drawn.

An association between use of solvents and paint and childhood leukaemia has also been investigated extensively. Scélo et al. (2009) and Bailey et al. (2010b) find some evidence of an increased risk in certain exposure situations, but the data do not give a consistent picture overall.

For post-natal exposure, the list of suspect chemicals is much longer: asbestos (Kishimoto et al. 1988, Pasqualetti et al. 1991), bioflavonoids (particularly topoisomerase II inhibitors such as quercetin) (Strick et al. 2000), oil (with incomplete combustion) (Glass et al. 2003), ethylene oxide (Shore et al. 1993), fungicides (Menegaux et al. 2006), coal (with incomplete combustion) (Glass et al. 2003), hydrocarbons (Lowengart et al. 1987), solvents (Freedman et al. 2001), engine exhaust gases (Knox 2006, Weng et al. 2008), perchloroethylene (Lynge et al. 1997), the insecticide permethrin (Borkhardt et al. 2003), incense (Lowengart et al. 1987) and tungsten (Sheppard et al. 2007). As with *in utero* exposure, there are some indications that pesticides may be significant (Bailey et al. 2010a, van Maele-Fabry et al. 2011, Turner et al. 2010), but here too, the results are far from consistent. It is also possible that as leukaemia development is suspected to be a multifactorial process, it is the interaction between several chemicals which may cause leukaemia.

Numerous drugs are suspected to trigger childhood leukaemia. This applies especially to many of the drugs used in chemotherapy, although it is particularly difficult, in this context, to identify the actual trigger as a mix of drugs is generally administered (Vega-Stromberg 2003). Other possibly problematical drugs are the analgesic dipyrone (Pombo-de-Oliveira and Koifman 2006, Emerenciano et al. 2007), hormonal treatment because of infertility (Schüz et al. 1999), head lice treatments containing allethrin, lindane or pyrethrum (Meinert et al. 2000, Menegaux et al. 2006), and laxatives containing anthraquinone (Wen et al. 2002). A link between neonatal administration of vitamin K and an increased risk of developing leukaemia is often hypothesised (Passmore et al. 1998); however, here too, no firm conclusions can be drawn, as recent analyses provide no convincing evidence to confirm this hypothesis (Roman et al. 2002).

6.2 Electromagnetic fields

The International Agency for Research on Cancer (IARC) allocates low-frequency magnetic fields to the category “possibly carcinogenic to humans” (Group 2B) (IARC 2001). This classification is based mainly on two separate meta-analyses which found

an estimated summary relative risk of 2.00 (i.e. doubled) for children with estimated residential magnetic field exposures >= 0.4 μT (Greenland et al. 2000, Ahlbom et al. 2000). This finding was confirmed in a 2007 publication based on measurements of extremely low-frequency electromagnetic fields during night-time hours only (Merzenich et al. 2008); previous conclusions were mainly based on 24-hour or 48-hour measurements, weighted for the fact that children did not spend the entire time in their rooms. Kroll et al. (2010) and Kheifets et al. (2010) recently re-examined older data (Draper et al. 2005). Kroll et al. used a refined exposure measure and found an increased risk for leukaemia in the highest exposure group compared with the lowest exposure group (>= 0.4 μT vs < 0.1 μT; OR = 2.0; 95 % CI: 0.18-22.04), although not statistically significant. The data from the study by Kroll et al. were also part of a pooled reanalysis by Kheifets et al. which also reported an increased risk (>= 0.3 μT vs < 0.1 μT, OR = 1.44; 95 % CI: 0.88-2.36) which, again, was not statistically significant. Schmiedel and Blettner point out in an editorial (2010) that results are unstable if case and control numbers in the highest exposure group are small. At present, there is no known biological mechanism which would explain an association between leukaemia development and such low-frequency fields.

A number of ecological studies found an association between proximity to the nearest television and radio transmitter and incidence of childhood leukaemia (although some of these studies only commenced once a noticeable excess of cases of childhood leukaemia had been observed); an association was not reported, however, in the largest of these studies, which investigated cancer incidence near 20 television and radio transmitters in Great Britain (Dolk et al. 1997). A comprehensive case-control study in Germany also found no association (Schüz 2008). A significantly higher risk for leukaemia was found in a case-control study conducted in South Korea (Ha et al. 2007); however, this study observed no trend of increasing leukaemia risk with decreasing distance from residence to the nearest radio transmitter and no linear dose-response relation.

6.3 Infections and immune system development

It has long been hypothesised that the immune system plays a key role in the development of childhood leukaemia, and this is confirmed by numerous studies which investigate the significance of vaccinations (Dockerty et al. 1999b, Groves et al. 1999, Ma et al. 2005), allergic disorders (Wen et al. 2000, Spector et al. 2004, Rosenbaum et al. 2005, Wang and Diepgen 2005), infections (review in McNally and Eden 2004), breastfeeding (Kwan et al. 2004, Guise et al. 2005, Martin et al. 2005) and social contacts (Urayama 2008, Spix et al. 2009). Two influential hypotheses have been formulated in relation to leukaemogenesis and immune response.

Proceeding from the observation that excesses of childhood leukaemia were occurring in the area around the British nuclear reprocessing sites at Sellafield and Dounreay and the findings of the COMARE studies, that the radioactive discharges can be ex-

cluded as cause due to the low dose (less than 10% of the background exposure and thus, based upon current knowledge, more than 100 times too low to explain the excess cases), Kinlen postulates that the large influx of labour migrants from other regions into previously isolated populations could trigger an increase in leukaemia. According to this "population mixing" hypothesis, a large influx of (mainly urban) newcomers into a rural area previously unexposed to a specific, albeit as yet unidentified, infectious agent could trigger an epidemic of the infection and thus cause an aggregation of rare complications such as leukaemia (Kinlen 1993a, Kinlen 1993b, review in Kinlen 2010).

In favour of this hypothesis is the observation that in comparable examples of mixing situations which have no relation to nuclear energy and nuclear installations, leukaemia clusters of children have been observed, e.g. in rural new towns, areas around large rural (non-nuclear) construction sites (e.g. hydro-electric schemes), wartime evacuation of children to rural areas, rural areas where large numbers of servicemen were stationed, and rural communities from which many men worked away from home in the oil industry. In all these situations, clusters of childhood leukaemia were found (Kinlen 2010).

One argument against this hypothesis is that it has not so far been possible to identify or isolate an infectious agent or agents specifically associated with childhood leukaemia, although in light of the Kinlen hypothesis, various studies have attempted to discover a virus associated with leukaemogenesis (review in Eden 2010). Possible candidates have included the Epstein-Barr virus and human T-lymphotropic virus type I (HTLV-1), both of which are known to cause certain types of leukaemia and lymphoma. However, a characteristic of HTLV1 is that it is only known to cause leukaemia in adults and only affects T-cells; it is therefore unlikely to play a role in leukaemogenesis in children. Controversy surrounds the question whether adenovirus DNA is detected more frequently in blood samples taken at birth from children who later developed ALL compared with controls without the disease (Gustafsson et al. 2007, Honkaniemi et al. 2010). The role of bacterial infections in childhood leukaemia has also been investigated, with Helicobacter pylori in particular suspected to be associated with increased risk of childhood leukaemia (Lehtinen et al. 2005).

In contrast to Kinlen's hypothesis that the immune system's overreaction to a specific infectious agent may trigger leukaemia, Greaves argues that due to delayed development of the young immune system, leukaemogenesis can occur in response to various common infections. According to Greaves' "delayed infection" hypothesis (Greaves 1988, Greaves 2006), the pathogenesis of leukaemia is a two-stage event. As the first event, a mutation in B-cell precursors during pregnancy causes a preleukaemic cell to develop (see also Section 6.6). Following an immune stress such as a common infection in children whose immune system development has been delayed, perhaps due to lack of social contact or overzealous hygiene, the immune system overreacts,

boosting the number of preleukaemic cells and thus increasing the probability that the second mutation which is necessary for the further development of leukaemia will occur in one of these cells (second hit).

This hypothesis may explain the increased risk of childhood leukaemia observed with factors associated with affluence (and hence higher levels of hygiene), largely accounting for the observed peak incidence of ALL between 2 and 5 years of age, as well as the protective effect of frequent social contact in early childhood. Two of the factors which, in numerous studies, have very consistently been found to offer a protective effect against the risk of childhood leukaemia are daycare attendance or equivalent, and older siblings. Urayama (2010a) recently conducted a meta-analytic evaluation of daycare attendance and risk of childhood acute lymphoblastic leukaemia (ALL). The analysis comprised 14 case-control studies and a total of 6 108 cases and generated a combined OR estimate indicating that daycare attendance before diagnosis is associated with a reduced risk of childhood ALL (OR = 0.76, 95 % CI: 0.67, 0.87).

In a further study, conducted as part of the Northern California Childhood Leukemia Study (NCCLS), Urayama et al. (2010b) examined the relationship between three measures of early life exposure to infections – daycare attendance, birth order and common childhood infections in infancy – with the risk of ALL in non-Hispanic white and Hispanic children. The protective effect of daycare attendance and older siblings was only observed among non-Hispanic children, which the authors attribute to Hispanic children generally living with more children (siblings and non-siblings) in a household. A French study (Rudant et al. 2010) investigated the role of factors considered related to early stimulation of the immune system in the aetiology of childhood acute leukaemia. This registry-based case-control study included 734 leukaemia patients aged between 1 and 14 years and 1 494 controls. Protective (if not always statistically significant) effects were reported for birth order (p for trend < 0.0001), attendance at a daycare centre before age 1 year (odds ratio (OR) = 0.8, 95 % CI: 0.6, 1.1), prolonged breastfeeding (OR = 0.7, 95 % CI: 0.5, 1.0), repeated early common infections (OR = 0.7, 95 % CI: 0.6, 0.9), regular contact with farm animals (OR = 0.6, 95 % CI: 0.5, 0.8), and frequent farm visits in early life (OR = 0.4, 95 % CI: 0.3, 0.6).

6.4 High birth weight and other peri-natal factors

Many studies have established a high birth weight (more than 3.5 or 4 kg, depending on the study; Ross et al. 1997, Schüz 2002, Okcu et al. 2002, Spix et al. 2009) as a risk factor for childhood leukaemia. A recently published meta-analysis which included more than 16 000 childhood leukaemia cases generated an odds ratio (OR) of 1.35 (95 % CI: 1.24, 1.48) for all types of leukaemia (Caughey and Michels 2009). A study conducted as part of the United Kingdom Childhood Cancer Study (UKCCS) conclu-

ded that correcting for the fact that boys generally weigh more than girls at birth, an association between high birth weight and risk of leukaemia can be observed with girls (e.g. for ALL: OR=1.81 (95 % CI: 1.36-2.39) with birth weight above 4 kg) (Smith et al. 2009). The association between high birth weight and leukaemia risk remains even after birth weight is corrected for gestational age: children who were large for gestational age (LGA) at birth had a 1.66 times (95 % CI 1.32-2.10) higher odds of ALL (Sprehe et al. 2010). Based on the survey element of the KiKK Study, Spix et al. report an OR= 1.96 (95 % CI: 1.12-3.41) for childhood leukaemias with birth weight above 4 kg (Spix et al. 2009).

It is hypothesised that insulin-like growth factors (IGFs) in particular are a possible cause: circulating IGF levels are highly correlated with foetal growth, and IGFs are believed to play an important role in carcinogenesis due to their proliferative and antiapoptotic effects (Callan and Milne 2009, Smith et al. 2009, Caughey and Michels 2009). Irrespective of any specific tumour-promoting effect, the increased growth could simply boost the number of potentially leukaemia-initiating stem cells, or the pool of preleukaemic cells could be larger, resulting in a greater probability that leukaemia will occur. The gene for insulin-like growth factor IGF-2 is generally subject to imprinting, which means that only the paternal allele (inherited from the father) is expressed, while the maternal allele (inherited from the mother) is silenced. Loss of imprinting is associated with increased expression of the gene. Interestingly, a previous molar pregnancy[a] was identified as a risk factor for mothers whose children were diagnosed with leukaemia; for example, an analysis carried out as part of the UK Childhood Cancer Study found an increased risk for leukaemia generally (OR=2.5; 95 % CI: 1.1-6.1) and also for ALL (OR=5.2; 95 % CI: 1.9-14.7) (Roman et al. 2006). Loss of imprinting is known to be a possible cause of previous molar pregnancies.

Besides molar pregnancy and high birth weight, various other peri-natal factors were identified as potential risk factors during analyses carried out within the framework of the UK Childhood Cancer Study. They include, for example, hyperemesis gravidarum[b], polyhydramnios[c], maternal anaemia during pregnancy, and pre-eclampsia[d] (Eden 2010). The significance of these observations is still unclear. An association between dietary deficiency of folate during pregnancy and an increased risk of leukaemia in offspring has also been postulated (Wiemels et al. 1999, Thompson et al. 2001, de Klerk et al. 2008). However, recently published studies on the effects of folate sup-

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[a] Molar pregnancy: an abnormal form of pregnancy in which a non-viable, fertilised egg implants in the uterus and causes an overgrowth of placental tissues.

[b] Severe form of pregnancy-related nausea and/or vomiting

[c] An excess of amniotic fluid in the amniotic sac

[d] Hypertension (= high blood pressure) in pregnancy

plementation before and during pregnancy do not give a consistent picture. In a meta-analysis by Milne et al. (2010), the summary odds ratios (ORs) for folate supplementation were 1.06 (95 % CI: 0.77-1.48) with reference to no folate supplementation. On the other hand, genetic polymorphisms in the genes of folate metabolism are often identified as being associated with the risk of leukaemia, suggesting that folate metabolism may well play a role in leukaemogenesis (see also Chapter 7).

6.5 Other possible factors

Many other factors are suspected of playing a role, at least, in the development of childhood leukaemia. They include socioeconomic status (Raaschou-Nielsen et al. 2004, Lawlor et al. 2006; see also Section 3.2.3), sex (Belson et al. 2007) and diet (Peters et al. 1994, Ross et al. 1996, Spector et al. 2005). Here too, however, the data are highly inconsistently, as the reviews by McNally et al. show very clearly (McNally and Eden 2004, McNally and Parker 2006).

The role of socioeconomic status has become a complex issue. Whereas in the past, it was customary for women of high socioeconomic status to stay at home, with the result that their offspring had less social contact with other children (no attendance at crèches, nurseries, etc.) and were shielded as effectively as possible from all sources of infection, it is now more common for well-educated women to return to work soon after giving birth, with the result that their children have far more contact with other children and exposure to possible sources of infection. This change in lifestyle is clearly reflected in recent studies (Smith et al. 2006) and reviews (Adam et al. 2008), with an association between childhood leukaemia and socioeconomic status no longer being reported.

6.6 Possibilities for analysis of risk factors by molecular characterisation of changes in preleukaemic and leukaemic cells

Leukaemia has a lower rate of genetic mutation than most solid tumours. Mutations typically observed in leukaemia cells include translocations, deletions and changes in chromosome number. Clear evidence for in utero origin of several translocations associated with childhood leukaemia (*TEL-AML1, AML1-ETO, PML-RARA and CBFB-MYH11*) comes, for example, from studies of twins and analysis of Guthrie cards, or neonatal blood spots (Wiemels 2008, Smith et al. 2005, Gale et al. 1997). These studies also found that these translocations are present in newborns at a frequency that is around 100-fold greater than the risk of the corresponding leukaemia (Mori et al. 2002). This indicates that translocation alone is not sufficient for leukaemia and that at least one subsequent mutation is required (*second hit*).

Somatic mutations (i.e. mutations which do not occur in the germline) in preleukaemic and leukaemic cells contain information that is important for an understanding of leu-

kaemogenesis. From the mutation spectrum – or in the case of chromosomal aberrations, from sequencing of DNA breakpoints – conclusions can be drawn about the initial DNA damage and possibly an agent which might trigger leukaemia.

Mutations in the *GATA1* gene in Down's syndrome (DS) patients with AMKL or a variant of the disease which occurs in newborns, known as transient myeloproliferative disorder (TMS), are particularly well-investigated. Observation of newborns shows that these mutations can occur at least partially *in utero*. The mutational spectrum points to oxidation damage and cytosine deamination as potential causes of *GATA1* mutations (Cabelof et al. 2009). The authors suggest that the mechanisms of mutagenesis may be explained by altered biologic pathways in DS, including increased oxidative stress and aberrant folate metabolism, suggesting the possibility that trisomy 21 induces a "mutator phenotype"; furthermore, DNA repair capacity evaluated in DS and non-DS patient samples provided evidence that the base excision repair (BER) pathway is compromised in DS tissues (Cabelof et al. 2009). The probability of a second hit would be increased due to the mutator phenotype. Similar mechanisms may also be responsible for the mutations in JAK tyrosine kinase genes commonly observed in ALL associated with DS (Bercovich et al. 2008). By way of qualification, however, it must be pointed out that the hypothesis that trisomy 21 induces a mutator phenotype is difficult to reconcile with the observation that solid tumours seem to be underrepresented in DS patients.

The most heavily studied translocation subtypes are those involving the mixed lineage leukaemia (*MLL*) gene. These *MLL* translocations are common in two groups of patients –infants with AML and ALL, and patients with secondary leukaemias (generally, but not always, AML) after previous cancer treatment with topoisomerase II-inhibiting drugs. Topoisomerase II is an enzyme which can resolve DNA entanglements as it generates a transient double-strand break in DNA. Topoisomerase inhibitors block the subsequent re-ligation of ends and keep the enzyme covalently attached to the DNA end. In the subsequent repair of the DNA molecule, as with any repair of DNA double-strand breaks, misjoining can occur, causing translocations. The breaks within the *MLL* gene occur in an 8.3 kb breakpoint cluster region betweens exons 8 and 13 which contains topoisomerase II target sequences (Krivtsov and Armstrong 2007). At the junctions, nucleotides can often be observed which were not present in the parental molecules. These *non-templated* nucleotides point to the involvement of non-homologous end joining (NHEJ) in the development of translocations (Felix et al. 2006). The distribution of breakpoints is similar in leukaemia patients who are under the age of 1 and adults with leukaemias following chemotherapy. Thus it is hypothesised that maternal exposure to DNA topoisomerase II inhibitors during pregnancy – such as those occurring naturally in foods – may contribute to the risk of infant leukaemia (Ross 2008). This hypothesis is supported by case-control studies which involve retrospective collection of data on maternal dietary habits during pregnancy. There are major uncertainties in these studies, however. It would therefore be interesting to con-

duct *in vitro* studies to investigate their potential to induce MLL translocations (Barjesteh van Waalwijk van Doorn-Khosrovani et al. 2007).

The pre-natal origin of translocations *TEL-AML1, AML1-ETO, PML-RARA* and *CBFA2-MYH11* in some patients is now well-established. Furthermore, the distribution of breakpoints and fusion sequences point to a causative mechanism mediated by non-homologous end joining (NHEJ), with no involvement of sequence motifs which are known to be particularly prone to breakage. Fusion between *ETV6 (TEL)* and *RUNX1 (AML1)* generated by a t(12;21)(p13;q22) translocation occurs in around 25 % of all cases of childhood ALL and defines the largest genetic subgroup in childhood ALL. In both genes, breakpoint cluster regions (BCRs) have been identified: in the 15kb intron 5 of *TEL*, and in *AML1*, in the 155 kb intron 1 and in the 5.5 kb intron 2. Sequencing of DNA breakpoints has been difficult due to the extended size of the respective breakpoint cluster regions, and, in most studies to date, was therefore only performed for a small number of patients. In a recently published study, the authors characterised the genomic fusion site in 60 patients; they also included 49 published sequences from other publications in their analysis in order to be able to make more reliable statements about the distribution of breakpoints and the sequences of the fusion sites (von Goessel et al. 2009). The authors found no association between the breakpoints with sequence motifs that indicate site-specific recombination events, such V(D)J recombination or topoisomerase II-mediated processes. They also found no aggregation of retrotransposon elements or regions with potentially altered DNA structure (e.g. palindromes). The existence of microhomologies in part of the fusion sites was interpreted by the authors as an indication of involvement of faulty repair of DNA double-strand breaks, e.g. by NHEJ.

In ALL with *TEL-AML1* translocation, partial deletion of the p arm of chromosome 12 can often be observed as a secondary event. Among other things, the deletion affects the second copy of the *TEL* gene. As a result, the oncogenic potential of the *TEL-AML1* fusion protein is no longer reduced by a functioning *TEL* protein. Wiemels et al. sequenced nine del(12p) breakpoints in order to explore the aetiology of this genetic event (Wiemels et al. 2008). They reported a clear association of breakpoints with repetitive retrotransposon elements, which could not be explained by activation of these elements which are normally silenced by methylation during global hypomethylation. The presence of non-template nucleotides was observed at most breakpoints; this would suggest formation when terminal deoxynucleotidyl transferase was active. However, they found no other evidence of an involvement of aberrant V(D)J recombination. Microhomology was present at only two del(12p) breakpoints; nonetheless, the authors hypothesise a causative mechanism for deletion that is based on NHEJ.

Unlike the translocations discussed above, the translocation which yields a fusion between *E2A* and *PBX1* genes and occurs in approximately 5 % of acute lymphoblastic leukaemia cases occurs after birth; there is evidence of its post-natal origin during

faulty V(D)J recombination (Wiemels 2008). V(D)J recombination plays an essential role in the generation of functional antibodies and T-cell receptors. V(D)J recombination is initiated through the programmed induction of DNA double-strand breaks (DSBs) by the RAG endonuclease with deletion of chromosome sequences during subsequent joining. It is strongly regulated and only occurs during certain stages in B-cell and T-cell development. Specific recognition sequences normally determine the site-specificity of RAG-mediated breaks, but if cryptic sequences, similar to the recognition sequences, are present, faulty joining can occur. This mechanism is also under discussion as triggering 9p21 deletions in ALL. Novara et al. cloned 23 breakpoint junctions in 17 childhood leukaemia cell samples (Novara et al. 2009). They found that half of 9p21 deletion breakpoints were mediated by ectopic V(D)J recombination mechanisms whereas the remaining half were associated to repeated sequences, including some with potential for unusual DNA structure formation. Microhomology, which points to the involvement of non-homologous end joining (NHEJ), was rarely observed.

In summary, it can be concluded that DNA double-strand breaks, which always occur early on in the formation of structural chromosomal aberrations such as translocations, may have a variety of causes. There is evidence of subtype-specific differences, relating, for example, to the involvement of endogenous factors (such as faulty V(D)J recombination) or exogenous factors (such as topoisomerase II inhibitors or environmental noxae which cause strand breaks). There is therefore mounting evidence that leukaemia subtypes, which have characteristic predominant genetic and chromosomal mutations, differ not only in prognosis and responsiveness to specific treatment modalities but also in origin. Studies which aim to identify leukaemogenetic noxae may be limited in their informative value unless the observed cases are stratified according to subtype. Scélo et al. provide an example of a study which took account of cytogenetic subtype: these researchers found a significant association between exposure to paint and ALL involving structural chromosomal changes (translocations), primarily t(12;21), but found no association with ALL cases involving numerical chromosomal changes (Scélo et al. 2009).

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7 Genetic Predisposition to Childhood Leukaemia

Every cancer is, ultimately, a disease of abnormal gene function, as the new properties displayed by cancer cells compared with their precursors stem largely from genetic changes (mutations and chromosomal aberrations) in these cells. Another factor which is increasingly recognised as important is the change in gene expression caused by epigenetic changes (e.g. in DNA methylation patterns or histone modification patterns). The new properties can include, for example, increased and/or unregulated cell division, disrupted DNA damage response functions, or the ability to metastasise. It is now assumed that for a normal cell to develop into a cancer cell, several genetic or epigenetic changes are required in the genes of relevance to carcinogenesis.

In rare cases, a mutation of relevance to carcinogenesis, such as the functional loss of a tumour suppressor gene, may already be present in the germline, which means that it is present in virtually every cell in the body. This reduces the number of further mutations within the cell that are needed for cancer to develop and greatly increases the probability of carcinogenesis compared with the general population. Depending on the penetrance of the mutation, as many as 100 % of carriers of the germline mutation may develop cancer at some stage in their lives. This is known as high penetrance. Examples are retinoblastoma, caused by loss-of-function mutations in one of the two copies of *RB1*, and breast cancer, with individuals predisposed to breast cancer having a mutation in one of their two copies of *BRCA1*. With high penetrance, a clear familial aggregation of the cancer in question can usually be observed; it is then described as an inherited, or hereditary, disease.

If it is assumed that the genes whose function is impaired by mutation in an inherited disease are relevant generally to carcinogenesis, and if these genes have been identified, it is possible to investigate whether specific variations occur more frequently (or less frequently) in sporadic cases (i.e. when no familial aggregation is discernable) than among healthy subjects. The same applies to all genes whose products may be involved directly or indirectly in carcinogenesis. For example, the probability of cancer developing may be increased if functionality is impaired in genes which, although not playing a role in the development of cancer-specific cell properties, nonetheless determine the probability of cancer-relevant genes mutating. Examples are genes which play a role in detoxifying mutation-inducing substances.

Within a population, several variants (also known as alleles[a]) of every gene exist; these variants generally only differ from each other in the nucleotide exchange at a small

[a] The term "allele" – like so many terms used in genetics – has undergone a change of meaning since it was first coined. Derived from the Greek αλληλος (allelos), meaning "each other", it was originally used for both the maternal and paternal copies of the gene in sexually reproducing organisms, even though these copies could not be distinguished from each other using the methods available at the time. Today, however, the term is also used to describe all the variants of a gene (or a given chromosomal region) existing within a population.

number of polymorphic sites. These polymorphic sites are known as *single nucleotide polymorphisms* (SNPs). They are found every few hundred base pairs throughout the genome and lend themselves to straightforward molecular genetic investigation. In many cases, the gene variant is by no means uncommon within the population, but not all carriers go on to develop cancer. This is known as "low penetrance", which means that the probability of developing cancer is increased, but other genetic and/or environmental factors must come into play for cancer to develop.

This chapter describes genetic factors which have been identified as increasing the risk of childhood leukaemia. Susceptibility to childhood leukaemia – as with most diseases – is influenced by genetic factors. This is evident, for example, from the greatly increased incidence of leukaemia that is associated with certain inherited diseases and congenital syndromes. Even so, only a very small percentage (less than 5 %; Eden 2010) of children with leukaemia suffer from a predisposing inherited condition.

Identifying gene variants which exert a light to moderate influence on disease risk is not an easy task. Geographical and ethnic variations in leukaemia frequency in the general population or various subgroups may be caused in variations in these genetic differences. For example, the percentage of *TEL-AML1* translocations in B-cell ALL is around 50 % lower in Hispanics than in non-Hispanic whites in California (Aldrich et al. 2006), and it is unclear whether this variation in frequency is due to ethnic-specific/environmental risk factors or genetics. As the causative mechanisms for various leukaemia subtypes can vary, as can the relative frequency of gene variants in various ethnic groups, it is desirable for the patient group (cases) to be as homogeneous as possible in terms of leukaemia subtype and ethnicity, an aspect which has rarely been considered in research to date. In relation to leukaemia subtype, at least, it can be expected that in future, more detailed information about the genetic characteristics of leukaemia cells will increasingly be available for every patient, as these factors are playing an ever greater role in prognosis and treatment decisions. It must also be borne in mind that the risk-modulating activities of gene variants may only come into play if specific environmental factors, such as exposure to pesticides, are present simultaneously.

7.1 Genetic syndromes and inherited diseases

Down's syndrome (trisomy 21) is not an inherited disease but a congenital chromosomal anomaly which is associated with a markedly increased risk for childhood leukaemia. DS children have a 10- to 20-fold higher risk for developing acute lymphoblastic leukaemia (ALL) and acute myeloid leukaemia (AML) as compared with non-DS children, and these odds increase to 500-fold for acute megakaryoblastic leukaemia (AMKL) (Malinge et al. 2009, Xavier et al. 2009). Interestingly, their overall risk of developing childhood cancer, in particular solid tumours, is lower (Hasle 2001). The causes of the increased leukaemia risk associated with Down's syndrome are still unclear. The hypothesis that the additional chromosome 21 may play a direct

and functional role is supported by the fact that the presence of additional genetic material on chromosome 21 is often also observed in non-DS children with leukaemia, for example in subgroups with hyperdiploidy (i.e. additional chromosomes in leukaemia cells). It has not yet been conclusively demonstrated which genes on chromosome 21 are relevant, but *AML1/RUNX1* is a much-discussed candidate (Tefferi and Gilliland 2007). Molecular genetic analyses to identify the additional genetic mutations necessary for leukaemogenesis have detected specific mutations of the *GATA1* gene, for example, and chromosomal changes which frequently occur in leukaemia cells in children with Down's syndrome but not in non-DS childhood leukaemia cases (Xavier et al. 2009), which indicates the existence of specific causative mechanisms (see below). An increased susceptibility to leukaemia among paediatric patients with Klinefelter's syndrome, another chromosomal disorder, is debated controversially (Machatschek et al. 2004).

Whereas children with Down's syndrome account for a low percentage of paediatric leukaemia cases (comprising approximately 1 % to 3 % of total patients with childhood leukaemia, for example; Malinge et al. 2009), the inherited diseases associated with an increased incidence of leukaemia are very rare, making molecular characterisation more difficult. In the case of recessive[a] inherited disorders, heterozygous carriers of the relevant gene mutations may also have an increased risk of leukaemia.

Fanconi anaemia (FA) is an inherited recessive disorder caused by mutations in at least 13 genes, including *BRCA2*, a gene which plays an important role in breast carcinogenesis. The Fanconi anaemia (FA) pathway participates in a complex mechanism of interstrand crosslink (ICL) repair. This is a type of DNA damage caused by diepoxybutane (DEB) or mitomycin C (MMC), for example. It is unclear at present which of the body's own metabolites may cause DNA interstrand crosslinks. It is hypothesised that this repair mechanism may also be relevant for replication-dependent repair of other types of DNA damage (Moldovan and D'Andrea 2009). FA patients have an extremely high risk of AML, with earlier onset than in patients without FA. A study of German FA patients found an observed/expected ratio of approximately 800 for AML, with a maximum incidence of 1.4 %/year at the age of 20 (Rosenberg et al. 2008). Studies which investigated whether heterozygous carriers of mutations of FA genes have an increased risk for childhood AML have so far tended to produce negative results (Meyer et al. 2006).

Biallelic germline mutations in the *NBS1* gene are responsible for Nijmegen breakage syndrome (NBS), a rare disorder characterised by chromosome instability and hy-

[a] In recessive inherited disorders, the disease only occurs when both parental copies of the gene are functionally impaired. In heterozygous carriers, who have one functional and one non-functional copy of the gene, the disease does not manifest; however, due to an insufficiency of the functional gene product, they may show certain symptoms, such as a light to moderately increased susceptibility to cancer.

persensitivity to ionising radiation (IR). The Nbs1 protein plays a very important role in cellular response to DNA double-strand breaks. Around 40 % of NBS patients have developed a malignancy before the age of 21, displaying an elevated risk to lymphoma in particular (di Masi and Antoccia 2008). As to the question whether heterozygous carriers of a function-impairing mutation of the *NBS1* gene have an increased risk for childhood leukaemia, a literature review by di Masi and Antoccia (2008) shows that around 1.1-1.5 % of children with ALL are carriers of this mutation. Mosor et al. also identified combinations of polymorphisms (haplotypes) in the *NBS1* gene as significantly increasing susceptibility to the development of childhood acute leukaemia in otherwise healthy children (Mosor et al. 2008).

Ataxia telangiectasia (AT) is another very rare disorder, caused by mutations in both copies of the *ATM* gene in the germline. Symptoms include increased sensitivity to radiation, immunodeficiency, and an increased risk of cancer, which can be explained by the fact that the ATM protein plays a key role in the cellular response to double-strand breaks (DSBs) in the DNA. Around 10-15 % of patients develop a lymphoid malignancy in childhood or young adulthood, with a preponderance of T-cell tumours (Taylor et al. 1996). The data currently available on germline mutations in *ATM* in paediatric leukaemia do not give a consistent picture (Gumy-Pause et al. 2008). Liberzon et al. (2004) studied *ATM* gene involvement in leukaemic cells derived from 39 paediatric T-cell acute lymphoblastic leukaemia (ALL) and identified biologically relevant germline mutations in *ATM* in 8 of these samples.

Bloom syndrome (BS) is a rare autosomal recessive disorder characterised by short stature, sun sensitivity and a high predisposition to cancer. Cells from persons with Bloom syndrome exhibit a striking chromosomal instability. The *BLM* gene is a member of the *RecQ* gene family of helicases, with functions in homologous recombination, a mechanism for the repair of DNA double-strand breaks and faulty replication intermediates. BS patients in every age group have a greatly increased risk of developing a wide range of cancers, with an early age of onset relative to the same cancer in the general population. In an analysis of the first 100 cancers observed in 168 individuals registered in the Bloom's Syndrome Registry, it was found that around 25 % of patients developed leukaemia or lymphoma, with around half these cases occurring among children younger than 15 years of age (German 1997). In a case-control study, Broberg et al. (2009) found that specific polymorphisms in genetic variants of BLM and proteins that form complexes with *BLM*, such as *TOP3A* and *RMI1*, were associated with an increased risk for AML or myelodysplastic syndromes. As the cohort consisted solely of adult patients, however, the significance for childhood leukaemia is unclear. Two other genetic diseases – Werner syndrome and Rothmund-Thomson syndrome – are caused by mutations in other *RecQ* helicases, *WRN* and *RECQL4* respectively. An increased risk of leukaemia and lymphoma is under discussion for these conditions as well (Segel and Lichtman 2004).

Li-Fraumeni syndrome is an autosomal dominant[a] inherited disorder which greatly increases the risk of developing several types of cancer. Most families affected carry a germline mutation in the *TP53* gene, which codes for the well-known tumour suppressor p53. A study of a cohort of individuals from 28 families with *TP53* mutations found that the mutation is weakly associated with leukaemia, mainly in older persons (Birch et al. 2001).

Shwachman-Diamond syndrome (SDS) is an autosomal recessive inherited disorder which affects many parts of the body, particularly the bone marrow, pancreas, and skeletal system. It can also affect other organs. Persons with SDS have a marked propensity for myelodysplastic syndrome (MDS) and leukaemia, with an estimated risk of 19 % at 20 years (Shimamura 2006). Shwachman-Diamond syndrome results from mutations in the *SBDS* gene, and it is hypothesised that this gives rise in some way – still imprecisely characterised – to a mutator phenotype[b] (Maserati et al. 2009). Unlike the other conditions discussed above, SDS does not fall under the classical definition of the chromosomal breakage syndromes, but is associated with a very specific kind of karyotype instability.

Other inherited bone marrow failure syndromes which are associated with myelodysplastic syndrome (MDS) and leukaemia are dyskeratosis congenita, congenital amegakaryocytic thrombocytopenia, Kostmann syndrome and Diamond-Blackfan anaemia (Alter 2007). Despite the increased incidence, the number of leukaemia cases described in the literature among patients with these conditions is extremely low and the age distribution is broad.

Germline mutations in an allele of the *NF1* gene cause von Recklinghausen (type 1) neurofibromatosis, an autosomal dominant hereditary disease characterised by numerous neurofibromas and by spots on the skin (Koike and Matsuda 2008). Children with this condition have a predisposition for JMML (juvenile myelomonocytic leukaemia), with leukaemogenesis associated with inactivation of the second *NF1* allele. *NF1* encodes the protein neurofibromin, which modulates RAS signaling. The *PTPN11* gene carries the instructions for making a protein which helps regulate the activation of the RAS signaling pathway. Germline *gain-of-function* mutations in *PTPN11* are found in around half the patients with Noonan syndrome, a developmental disorder affecting multiple parts of the body, which is also associated with a predisposition to JMML.

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[a] In dominant inherited disorders, the disease manifests even if only one abnormal copy of the gene is inherited.

[b] With a mutator phenotype, the probability of mutations occurring in all genes in a cell is increased. As some of the potentially mutating genes are relevant to carcinogenesis, a mutator phenotype can result in a predisposition to cancer.

Besides cases of leukaemia that are associated with complex inherited syndromes, familial occurrence of leukaemias in ostensibly healthy persons can provide a useful resource for the identification of possible susceptibility genes, although the age at diagnosis in the families identified to date is heterogeneous and, overall, few children are affected (Segel and Lichtman 2004, Owen et al. 2008). To date, two culprit genes have been identified as having a role in familial leukaemia: mutations of the *CEBPA* gene, which codes for a transcription factor, segregate with familial acute myeloid leukaemia (AML) in an autosomal dominant pattern. Familial thrombocytopenia with predisposition to AML (FPD/AML) is an autosomal dominant hereditary disorder with mild to moderate bleeding disorders; germline mutations in *AML1* (*=RUNX1*) have been identified as the cause (Owen et al. 2008). Translocations in this gene are found in many types of leukaemia (see below). Around half the carriers of the mutations develop myelodysplastic syndrome or AML during their lifetime.

Table 7.1: Genetic syndromes and inherited diseases with an increased risk for childhood leukaemia (Luibrand 2010)

Genetic syndromes associated with an increased risk for childhood leukaemia
Down's syndrome: approx. 1/650-1 000 live births
Inherited diseases with an increased risk for (childhood) leukaemia (also in heterozygous mutation carriers in some cases); affected genes in parentheses
Fanconi anaemia (*FANCA, FANCB, FANCC, FANCD1 (=BRCA2), FANCD2, FANCE, FANCF, FANCG, FANCI, FANCJ, FANCL, FANCM and FANCN): approx. 3/1 000 000*
Nijmegen breakage syndrome (*NBS1*): rare, no accurate data available
Ataxia telangiectasia (*ATM*): approx.1/300 000 live births
Bloom syndrome (*BLM*): rare, no accurate data available
Li-Fraumeni syndrome (*TP53, CHK2*): rare, no accurate data available
Shwachman-Diamond syndrome (*SDS*): rare, no accurate data available
Neurofibromatosis (type 1) (*NF1*): approx. 1:3 500
Noonan syndrome (*PTPN11*): 1: 1:1 000-1:2 500 live births
Familial AML (*CEBPA*): rare, no accurate data available
Familial thrombocytopenia with predisposition to AML (*AML1=RUNX1*): rare, no accurate data available

In summary, it can be concluded that despite the large number of genetic syndromes and inherited diseases associated with an increased risk of childhood leukaemia (Table 7.1), the number of paediatric leukaemia cases with these syndromes is very low, with the exception of Down's syndrome and Nijmegen breakage syndrome. For that reason, very few informative quantitative analyses of increased risk and mechanistic studies have been conducted.

7.2 Analysis of polymorphisms in candidate genes

Genes of possible relevance to leukaemogenesis are not only identified from inherited diseases. The existence of a growing body of knowledge about cancer-relevant metabolic pathways and polymorphisms in the relevant genes, and the fact that modern techniques make it easier to investigate possible associations between individual gene variants and disease, have focused attention on the role of possible predisposing genetic factors in the aetiology of childhood leukaemia in recent years (reviews in Smith et al. 2005, Sinnett et al. 2006, Chokkalinagam and Buffler 2008). In those studies on childhood leukaemia which have found a significantly increased childhood leukaemia risk when specific alleles are present, these increases have generally been relatively slight (odds ratio: OR<2). The literature on genetic predisposition to childhood leukaemia has focused mainly on immune function and response to infection, folate metabolism, transport, activation and detoxification of carcinogenic xenobiotic substances, oxidative stress, and DNA repair, with more data being available for ALL than AML (Chokkalingam and Buffler 2008). An important factor which has not always received adequate attention is the considerable heterogeneity of leukaemia types, which are presumably associated with heterogeneous causative mechanisms. In searching for associations between disease and gene variants, it is recommended that the case groups investigated should be as homogeneous as possible.

Folate metabolism

Folate is critical in DNA synthesis and repair and in methylation processes. Deficiencies in folate contribute to chromosomal damage. In at least some of the studies conducted, folate supplementation before and during pregnancy was shown to protect against childhood ALL in offspring (de Klerk and Milne 2008). However, the findings of studies on an association between polymorphisms in genes involved in folate metabolism and childhood leukaemia are controversial (de Klerk and Milne 2008, de Jonge et al. 2009). Polymorphic variants at positions *C677T* and *A1298C* in *MTHFR* have been particularly well-investigated in relation to leukaemia risk. Several studies have shown that both variants decrease susceptibility to lymphoid leukaemia in children and adults, whereas other studies found no effect. A possible cause of the discrepancies is that the protective effect is only present under conditions of folate deficiency. Krajinovic et al. tested this hypothesis by investigating the effect of the

supposedly protective variants in separate groups of Canadian children born before and after 1996, the year of the introduction of the Health Canada recommendation for folic acid supplementation in pregnancy. It can thus be assumed that folic acid intake improved after 1996. The authors observed that the protective effect of the tested *MTHFR* variants was indeed present only in children born before 1996 (Krajinovic et al. 2004).

Variants in genes whose products are involved in the metabolism of carcinogens

Most chemical carcinogens can only interact with DNA and cause mutations after they are metabolised in the body. The metabolism of xenobiotic substances may be divided into two phases. In phase I, enzymes introduce reactive or polar groups into xenobiotics. These modified compounds are then conjugated to polar compounds in phase II reactions, facilitating excretion in urine or bile. If specific variants of genes of phase I or phase II enzymes modulate the cancer risk, this points to a role of their substrates in carcinogenesis, especially in those variants which influence enzyme activity. The literature includes a large number of studies which investigate an association between polymorphisms in genes involved in metabolism of xenobiotic substances and carcinogenesis. Often, the results are inconsistent, which can be explained *inter alia* by the fact that certain alleles only have a risk-modulating effect if they are present alongside other risk-modulating alleles and/or relevant environmental factors.

The cytochrome P450 family comprises a group of phase I enzymes with varying substrate specificity, e.g. *CYP1A1* for polycyclic aromatic hydrocarbons, and *CYP2E1* for nitrosamines, benzene, ethanol, acetone, halogenated solvents and various drugs (e.g. paracetamol). *CYP1A1* alleles with increased enzyme activity (*CYP1A1*2A, CYP1A1*2B*) are associated with increased formation of DNA adducts and tumour risk. A number of studies showed some evidence of an association between a *CYP1A1*2A* allele with a risk of childhood ALL, whereas others showed no effect (Chokkalingam and Buffler 2008, Sinnett et al. 2006).

The glutathione S-transferases (GST) are a family of enzymes with defined substrate and tissue specificities. The genes coding for *GSTT1* and *GSTM1* exhibit a deletion polymorphism that in case of homozygosity leads to the absence of proteins. This is a fairly common genotype in humans, with 50 % of Caucasians being homozygous for null *GSTM1*, and 20 % homozygous for null *GSTT1*; a meta-analysis of published studies on the effect of the deletion polymorphisms found that there appears to be an association with a modest but significant increase in the risk of ALL; however, a smaller number of studies on the possible influence of *GSTP1* genotype on childhood ALL all had negative results (Ye and Song 2005). More recent studies, however, point to an association between the *GSTM1* deletion allele and paediatric ALL (Chokkalingam and Buffler 2008), whereas the *GSTT1* deletion allele apparently has no effect. Various polymorphisms of *GSTP1* are known to exist, for which an increased risk has also been described (Sinnett et al. 2006).

The N-acetyltransferases (*NAT1 and NAT2*) are highly polymorphic and are involved in both activation and inactivation reactions of numerous carcinogens, such as heterocyclic amines from tobacco smoke and smoked meat; in both genes, there are alleles which code for fast or slow acetylator phenotype. Various alleles of *NAT2* are under-/over-represented in children with ALL; alleles with slow acetylator genotype are associated with increased risk. By contrast, various *NAT1* alleles appear to have no effect (Sinnett et al. 2006).

The *NQO1* gene encodes NAD(P)H:quinone oxidoreductase, a phase II enzyme which is involved in the detoxification of carcinogenic quinones, such as benzene metabolites. It protects against oxidative stress and also stabilises the p53 tumour suppressor protein. There is particular interest in *NQO1*2*, which results in an amino acid change at codon 187 that is associated with a loss of enzyme activity. Around 3 % of the European population has almost undetectable enzyme activity of the homozygous variant genotype (*NQO1*2*) (Kiyohara et al. 2005), and various studies among adults point to an increased risk for acute leukaemia among carriers of this allele. A recent meta-analysis of case-control studies that examined the association between *NQO1*2* and childhood leukaemia found an increased risk for subtypes of acute leukaemia (AML and ALL) with having at least one copy of the *NQO1*2* allele in a subset of cases with MLL translocations (Guha et al. 2008). An MLL^+ genotype is very common in infants aged < 12 months with leukaemia. The authors hypothesise that these results are biologically plausible, as MLL^+ leukaemia is associated with topoisomerase II inhibitors and many of the compounds that are metabolised by *NQO1* also inhibit topoisomerase II. However, the meta-analysis has attracted criticism from other authors (Lanciotti and Dufour 2009).

The multidrug resistance 1 gene (*MDR1*) encodes a membrane transporter which plays an important role in protecting cells against lipophilic xenobiotics by way of an ATP-dependent cellular efflux mechanism. Although overall, the studies have produced inconsistent results (Chokkalingam and Buffler 2008), a study carried out among Californian children which investigated four polymorphisms in *MDR1* found no significant association with childhood ALL, but a specific combination of polymorphisms (haplotype) showed a strong protective effect against the ALL risk associated with insecticide exposure (Urayama et al. 2007).

Immune function

The search for risk-modulating polymorphisms in immune system genes is influenced by Greaves' hypothesis that in the pathogenesis of ALL, particularly pre-B-cell ALL in the 2-5 year age group, an overreaction to a common infection in children plays an important role by promoting the selective survival of pre-leukaemia cells and thus increasing the probability of further mutations (Greaves 2006). The major histocompatibility complex (MHC) is a large cluster of genes which are relevant, *inter alia*, to

immune response. The MHC genes are traditionally divided into classes, each with three polymorphic genes: MHC class I (HLA-A, HLA-B, HLA-C) and class II genes (HLA-DR, HLA-DQ, HLA-DP). These cell surface glycoproteins bind and present peptide antigens to T-cells. Class I MHC proteins bind and present endogenous peptides such as those derived from the degradation of proteins in the cell. By contrast, peptides derived from exogenous proteins which were absorbed by the cell from phagocytosis are presented at the cell surface by class II MHC proteins. A number of diseases are associated with specific alleles in the HLA genes, mainly those with an autoimmune pathogenesis. It is hypothesised that these diseases occur as a result of infection, when sequence similarities between endogenous and pathogen-derived peptides (molecular mimicry) activate autoreactive T-cells which then attack the body's own structures.

Taylor et al. reported that susceptibility to B-cell precursor ALL (BCP ALL) is associated with *HLA-DPB1* alleles having glutamic acid at position 69 (Taylor et al. 2008, 2009). Using bioinformatic methods, they first predicted the sequence of peptides that could be presented by the relevant HLA molecules and then the pathogens whose proteins could be processed into the relevant peptides. This search for potential pathogens based on the immune system molecules that they recognise is known as reverse immunogenetics. Taylor et al. hypothesise that after infection with human cytomegalovirus (CMV), an autoimmune response to alpha-1-integrin (CD49a) is induced. The integrins are a widely expressed and diverse family of heterodimeric adhesion receptors that play a major role in cell-matrix and cell-cell interactions. Alpha-1-integrin non-covalently associates with beta-1-integrin to form the α1/β1 complex, VLA-1 (CD49a/CD29) which is expressed by bone marrow stromal myofibroblasts. These cells support the growth of human B-cell precursors. Destruction of stromal myofibroblasts by cytotoxic T-cells could compromise the adhesion of normal B-cell progenitors to stroma and could account for the selective survival of pre-leukaemia cells. As envisaged by the Greaves hypothesis, the CMV infection with subsequent destruction of the stroma cells would constitute the second hit.

7.3 Genome-wide association studies

Besides hypothesis-driven studies of candidate genes, the first genome-wide association studies have now also been carried out (Levine 2009). In these studies, SNPs in groups of cases and healthy controls are analysed in order to determine whether specific SNPs occur more or less frequently among persons with the disease compared with healthy controls, indicating that they may be associated with the disease. SNP analysis can be carried out using high-throughput procedures, enabling several 100 000 polymorphisms per individual to be tested genome-wide. Specific SNPs may be causally linked to the aetiology of the disease being studied if they change the function or number of the gene product concerned. However, they may also be present

with an unexpectedly high (or low) degree of frequency together with another – i.e. causal – mutation, indicating a coupling disequilibrium, making it more difficult to pinpoint the cause of the disease.

Papaemmanuil et al. investigated a total of 907 childhood ALL cases of Western European origin and 2 398 controls (Papaemmanuil et al. 2009). They identified 10 SNPs at 3 different loci that were significantly enriched in ALL cases as compared to controls. The first at-risk locus is associated with *IKZF1* (Ikaros family zinc finger 1), a gene that encodes a protein which has an important role in lymphocyte development. It is often somatically deleted in ALL tumour cells, suggesting a causal link between certain alleles in *IKZF1* and the development of ALL. The second relevant locus contains gene *ARID5B* (AT rich interactive domain 5B), which encodes a transcription factor involved in embryogenesis and growth regulation. This gene had not previously been shown to be involved in the pathogenesis of ALL, but may be involved in B-cell differentiation. The third locus related to gene *CEBPE* (CAAT/enhancer binding protein epsilon), which is occasionally involved in translocations in B-cell precursor ALL. Treviño et al. studied 317 childhood ALL patients of European origin and 17 958 controls, also of European origin (Trevino et al. 2009). These authors identified 18 SNPs (out of 307 944) whose allele frequency differed significantly between cases and controls. The 18 SNPs were assigned to 12 genes, including *ARID5B* and *IKFZ*. Both groups found some evidence that specific SNPs can be assigned to specific ALL subtypes, with high frequency of risk alleles of *ARID5B* in B-hyperdiploid ALL compared with other subtypes, for example.

Outlook: In parallel to genome-wide association studies, it is hoped that the increasing availability of state-of-the-art techniques such as whole-genome or transcriptome sequencing and genome-wide analysis of gene expression patterns will offer further insights into genetic factors which increase susceptibility to leukaemia (Ziegelberger et al. 2011). International cooperation should make it possible to identify a sufficiently large number of cases and controls so as to permit stratification in subgroups, based, for example, on leukaemia subtype, disease-relevant translocation in leukaemic cells, or exogenous risk factors.

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List of Abbreviations

ACCIS	Automated Childhood Cancer Information System
ALL	Akute lymphatische Leukämie
AMKL	Akute megakaryoblastische Leukämie
AML	Akute meyeloische Leukämie
ANLL	Akute nichtlymphatische Leukämie
APL	Akute promyelozytäre Leukämie
ARID5B-Gen	AT-rich interacting domain 5B-Gen
AWMF	Arbeitsgemeinschaft der Wissenschaftlichen Medizinischen Fachgesellschaften e.V.
CLL	Chronische lymphatische Leukämie
CML	Chronische myeloische Leukämie
COMARE	Committee on Medical Aspects of Radiation in the Environment
DKKR	Deutsches Kinderkrebsregister
EAR	Excess Absolute Risk
ERR	Excess Relative Risk
FPD/AML	Familial platelet disorder with predisposition to acute myelogenous leukemia
HLA	Human Leukocyte Antigen
IARC	International Agency for Research on Cancer der WHO
ICCC	International Classification of Childhood Cancer
ICD	International Classification of Diseases
ICD-O	International Classification of Diseases for Oncology
JMML	Juvenile myelomonozytäre Leukämie
KIKK-Studie	Epidemiologische Studie zu Kinderkrebs in der Umgebung von Kernkraftwerken
LL	Lymphoide Leukämie
LNT	Linear-No-Threshold
LSS	Life Span Study
MDS	Myelodysplastische(s) Syndrom(e)
ML	Myeloische Leukämie
MLL-Gen	mixed-lineage leukemia Gen
NHL	Non-Hodgkin-Lymphome
OR	Odds Ratio
OSCC	Oxford Survey for Childhood Cancer
RAG	recombination activating gene
RR	Relative Risk
SIR	Standardized Incidence Ratio
SMR	Standardized Mortality Ratio
SNP	single nucleotide polymorphisms
UKCCS	United Kingdom Childhood Cancer Study
V(D)J-Rekombination	Variable, Diverse, and Joining gene segments recombination

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