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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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CONTENTS

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 (normal 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%[1]. 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).

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

[1] 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.

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 prenatally, 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[1] (2006) and ICRP[2] 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 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

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

[2] International Commission on Radiological Protection

children up to the age of 5, in the vicinity of nuclear power plants (within a 5 km radius).[1] 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 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.

[1] 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.

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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