Leukaemia Incidence in Children and Adults in the Regions of Russia Most Highly Contaminated after the Chernobyl Nuclear Power Plant Accident

Dissertation
zum Erwerb des Doktorgrades der Medizin
an der Medizinischen Fakultät der
Ludwig-Maximilians-Universität zu München

vorgelegt von

Susanne Isabel Becker
aus
Frankfurt am Main

2003

Aus dem
Institut für Medizinische Informationsverarbeitung, Biometrie und Epidemiologie
der Ludwig-Maximilians-Universität München
Vorstand: Prof. Dr. med. K. Überla

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Mit Genehmigung der Medizinischen Fakultät
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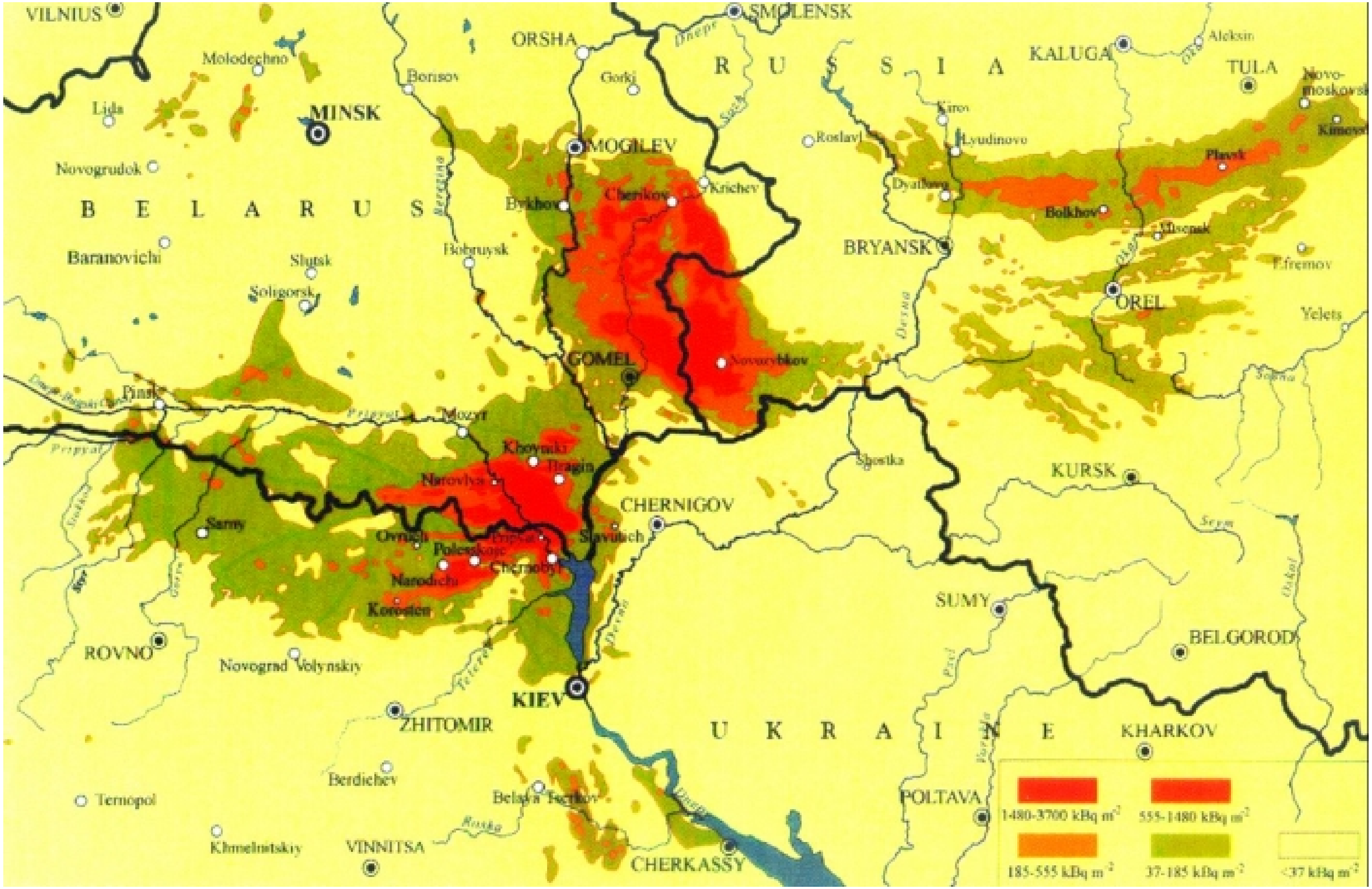
Tag der mündlichen Prüfung:.....06.11.2003.....

TO THOSE WHO HAVE SUFFERED AND WILL CONTINUE TO SUFFER
THE CONSEQUENCES OF THE CHERNOBYL NUCLEAR POWER PLANT ACCIDENT


VILNIUS
SMOLENSK
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Kirov
Roslavl
Lyudinovo
MOGILEV
Kimovsk
Novogrudok
Plavsk
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Pinsk
Pripyat
Mozyr
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Shostka
Bragin
KURSK
Narovlya
CHERNIGOV
Sarny
Ovruch
Pripyat
Slavutich
Polesskoje
Chernobyl
Narodichi
Korosten
SUMY
ROVNO
BELGOROD
Novograd Volynskiy
KIEV
ZHITOMIR
U K R A I N E
KHARKOV
Berdichev
Belaya Tserkov
POLTAVA
Ternopol
Khmelnitskiy
VINNITSA
CHERKASSY
Dnepr
1480-3700 kBq m⁻²
555-1480 kBq m⁻²
185-555 kBq m⁻²
37-185 kBq m⁻²
<37 kBq m⁻²

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1. INTRODUCTION

Leukaemia, especially the acute types predominant in children, may be caused by ionizing radiation. The large scale epidemiological studies of the cohort that had been exposed in Hiroshima and Nagasaki (Life Span Study) show a significantly increased risk of leukaemia among the survivors [TOM 93]. Altogether, 290 cases of leukaemia were observed between 1950 and the end of 1987 among 93 696 survivors accounting for 2 778 000 person years [PRE 94]. A dose could be attributed to 231 of the 290 cases. Of the 231 cases taken into the analysis, 75 cases were estimated to be due to the radiation [PRE 94]. This induction of tumours of the haematopoetic system is the most important stochastic health effect even at low radiation doses [SHI 95, PIE 96].

The relative risk (RR) of leukaemia (ALL, AML and CML – no increase of CLL has been observed in Japan) at 1 Sievert is 6.13, as compared to a RR of all solid tumours at 1 Sievert of 1.63. The relative risks at 1 Sievert for the different types of leukaemia vary from 4.3 (AML) to 7.2 (CML) and 10.1 (ALL) [PRE 94, THO 94]. The *excess* relative risk of leukaemia at 1 Sievert (ERR_{1Sv} 5.13) is 8.14 times the excess relative risk of all solid tumours at 1 Sievert (ERR_{1Sv} 0.63) [PRE 94]. This risk induction is detectable for doses of 200 mSv or more [DOL 98], whereas the risk at lower doses is disputable, but may be present from as little as 50 – 100 mSv [PIE 96]. The general pattern of cancer incidence in the exposed Japanese cohort showed men to have higher relative risks than women and the risks tended to be higher for those exposed at younger ages [PRE 94]. A British study of children whose mothers had been x-rayed during pregnancy found that the leukaemia risk up to the age of 15 was 40% above the spontaneous rate even at doses of 10-20 mSv [STE 56].

Due to problems with case ascertainment and the determination of population size in Hiroshima and Nagasaki it is impossible to compute risk estimates for leukaemia for the years before 1948 [PRE 94]. When the Life Span Study cohort was first established in 1950, however, an increase of leukaemia was evident and peaked in the period 1950-1953 [SHI 95]. Estimates on leukaemia incidence in the years 1948-1950, however, already show an increase in incidence rates which are based on untyped cases obtained from the Leukaemia Registry [FOL 52]. An increase of leukaemia incidence may thus be expected after a latency of about two years with the highest risk occurring five to eight years after irradiation [PRE 94], whereas the incidence of solid tumours begins to increase only after a latency of ten years.

Even more than 30 years after the bombings, the incidence rates both of leukaemia (except CLL) and solid tumours among those affected are higher than in the remainder of Japan [PRE 94, THO 94].

1.1. LEUKAEMIA – A SHORT OVERVIEW

1.1.1. DEFINITION

The term *leukaemia* goes back both to Rudolph Virchow and John Bennett who described the predominance of leukocytes in the blood of patients with chronic myeloid leukaemia (CML) as *white blood* first in 1845 [BEN 03, VIR 03]. *Leukaemia* designates several malignant disease entities of the haematopoetic or lymphopoetic system with uncontrolled clonal proliferation and/or altered pathways of apoptosis at distinct stages of haematopoesis.

1.1.2. CLASSIFICATION

Acute myeloid leukaemia (AML) and *acute lymphoblastic leukaemia* (ALL) are clonal disorders of early myeloid or lymphoid precursors. ALL can be distinguished immunologically into B-cell or T-cell precursors of different stages of differentiation. There are different prognostic subgroups according at least partly to certain cytogenetic alterations.

AML can be classified morphologically into 6 different types. However, there are several known cytogenetic aberrations in AML which are prognostically more important than the morphological subtype. AML with balanced translocations (e.g. t(15;17), t(8;21)) belongs to the low risk group concerning a relapse after therapy, whereas AML with complex karyotypes with gain or loss of chromosomal material is prognostically unfavourable. Generally, AML is classified into primary and secondary forms. AML occurring after chemo- or radiotherapy or in the course of myelodysplastic syndromes is defined as secondary leukaemia. Radiation-associated Leukaemia shows complex karyotypes more frequently than leukaemia after chemotherapy and therefore has a worse prognosis. Whether AML which was induced as a consequence of a nuclear accident belongs to this risk group remains to be determined.

Chronic myeloid leukaemia (CML) is a clonal disease of an early pluripotent stem cell with a characteristic cytogenetic defect, the Philadelphia chromosome, which is the result of a balanced reciprocal translocation between chromosome 9 and 22. On the molecular level, abl is translocated from chromosome 9 to the breakpoint cluster region (bcr) of chromosome 22. The resulting hybrid gene bcr-abl leads to the expression of a deregulated tyrosinkinase. The consequences of its activity are:

- alteration of adhesion to the bone marrow stroma
- activation of mitogenic signals
- inhibition of apoptosis
- deregulation of inhibitory proteins

This cytogenetic defect appears at such an early stage of haematopoesis that it affects granulopoesis (including eosinophils and basophils), as well as erythropoesis, megakaryopoesis, B-lymphocytes and – in rare events – even T-cells. The bcr-abl rearrangement can then be found in all of these cells. Additional cytogenetic events in the course of the disease lead to its progression, resulting in an accelerated phase and finally a blast crisis [WAT 03].

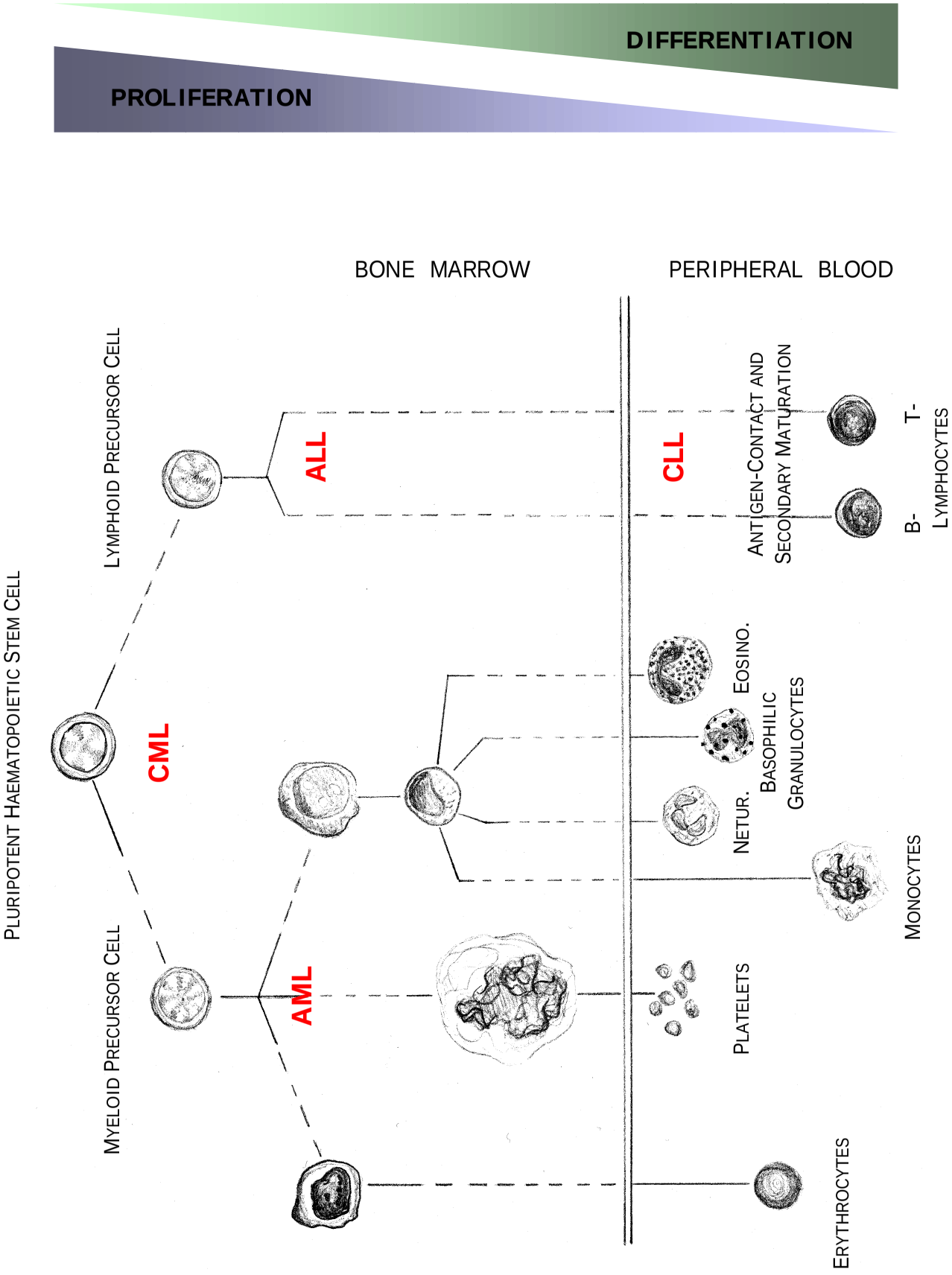


Fig. 1.1 Physiological haematopoesis and point of origin of different types of leukaemia

Graphic: Susanne Becker

Leukaemic cells in *chronic lymphatic leukaemia* (CLL) appear mostly as morphologically mature B-cells. The stage of differentiation of the neoplastic cells corresponds to a circulating mature but antigen-naive B-cell. These clonal B-cells are immunoincompetent, the proliferation is slow and the survival longer than in normal B-cells. The disease is frequently associated with autoimmune phenomena such as autoimmune haemolysis or immune thrombocytopaenia. The risk of secondary solid tumours is enhanced compared with normal controls. Although there are certain cytogenetic alterations associated with a worse prognosis, the course of the disease is generally benign in comparison to the other types of leukaemia [WAT 03].

1.1.3. EPIDEMIOLOGY

Leukaemia incidence rates in children are astonishingly similar throughout the world. The mean annual age-standardized incidence rates in the 28 European registries presented by IARC lie between 3.3/100 000 (Bulgaria) and 5.3/100 000 (Denmark). The risk is slightly higher for boys than for girls. About 75-80% of leukaemia in children is ALL, 20-25% AML. The share of chronic leukaemia does not exceed 2-3%, most of which are of myeloid form [PAR 98]. However, a few cases of CLL are also documented [YOF 90, SON 83]. Acute leukaemia shows a characteristic peak in incidence between the ages of two and five years. The age-specific incidence subsequently declines to about 2/100 000, where it remains stable during childhood and adolescence [DKR 00].

In adults, the distribution of ALL and AML is exactly the opposite as in children: 80% of acute leukaemia type as AML, 20% as ALL. The mean age for incurring AML is 62 years, whereas the incidence of ALL, apart from the peak at age three, remains moderate at about 2/100 000 [IME 98, SEE 03].

Predominant in adults are the chronic forms of leukaemia, CLL and CML, which occur in a ratio of 2:1 respectively. There is a male predominance for both [FIN 92]. The mean incidences in adults are 2-3/100 000 for CLL and 1-1.5/100 000 for CML [IME 94]. Age-specific incidence rates increase with age. This increase starts after the age of 40 and the acceleration is about twice the rate in CLL than in CML [SEE 03]. Figure 1.2 shows the age-specific incidence rates for all leukaemia and for the different forms separately.

Despite their incurability, the overall prognosis is best for chronic leukaemia. The median survival of patients with CLL is more than five years [TEF 92], based on a survival between 2 (stage III) and 13 (stage 0) years depending on the stage [RAI 90]. Patients with de novo CML show a median survival of 3.5 years [COR 95]. For 1985-1989, EUROCARE reports weighted age-standardized 5-year survival rates for Europe of 63% (CLL), 31% (CML), 25% (ALL), 10% (AML). Survival had improved compared with 1978-1980 for CLL, AML and ALL, only CML showed little improvement. Poorer survival rates are reported for the Eastern European countries. The relative survival declines with age and this effect is most marked in patients with acute leukaemia. [CAR 98].

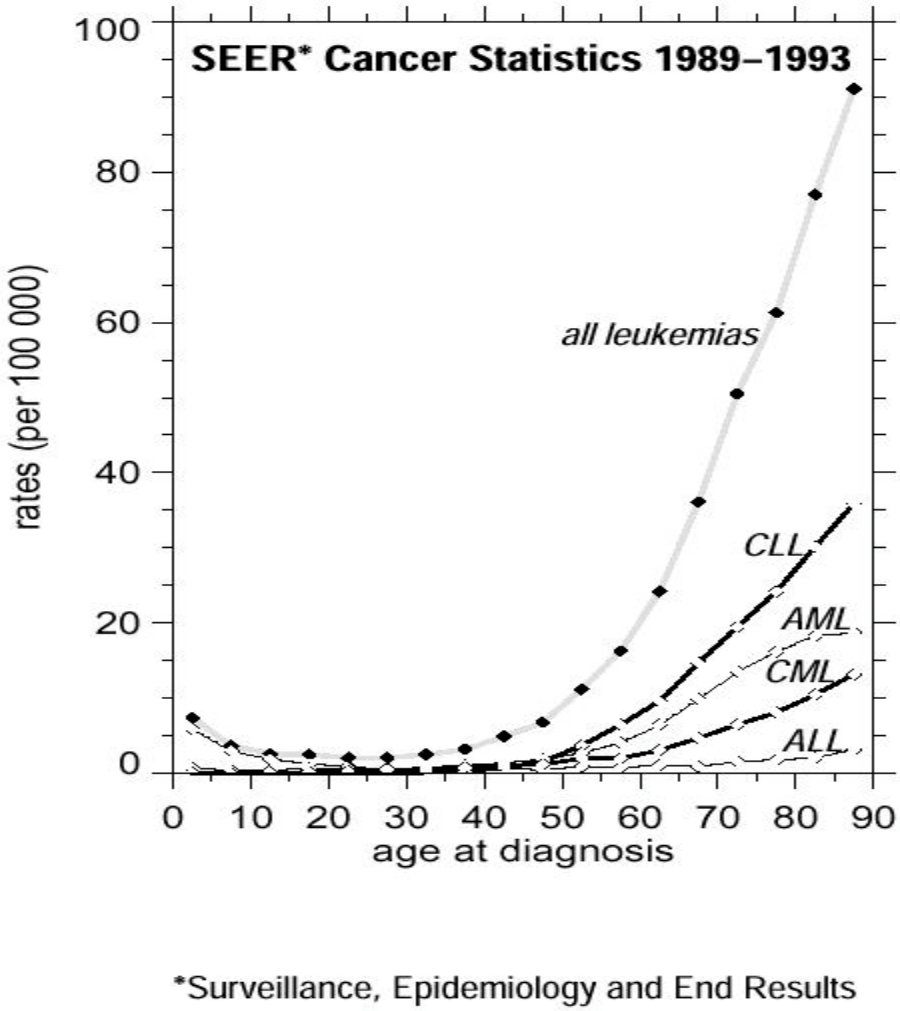


Fig 1.2 Age-specific incidence rates for leukaemia [SEE 03] (*SEER: Surveillance, Epidemiology and End Results). Figure by Elke Nekolla.

1.1.4. RISK FACTORS OTHER THAN RADIATION

Apart from radiation, which has been shown to increase the risk of CML, AML and ALL in various cohorts [LIT 99b, WIC 99] – an influence on CLL is recently also being discussed [LAM 98, LOU 98, GLU 01, IMA 01] – various substances and other factors may have a role in inducing leukaemia.

The past decades have seen remarkable progress in the understanding of the biological features and, consequently, in the therapeutic approaches towards leukaemia. Nevertheless, no one main risk factor has so far been identified. Even the established risk factors often increase the risk only marginally and studies concerning a multitude of possible risk factors show contradictory results. Anyway, under the assumption of a model of tumourgenesis with - at least - one mutation and one promotion [GRE 93b] it is implausible to assume the influence of but one causal factor.

For acute leukaemia, there are a number of established risk factors such as ionizing radiation, certain genetic constellations like Down's syndrome, Ataxia teleangiectasia, Fanconi's anaemia, type I neurofibromatosis, HTLV I (for adult T-cell leukaemia). Other factors are still under discussion: electromagnetic fields, factors associated with the immune system like little early infections or allergies and immunisation (both protective) and chemicals like benzene or pesticides [BEC 02, SCH 02]. As to acute leukaemia in children, the idea that infections might play a role in their induction had been discussed at the beginning of the last century, but was later dismissed. This idea has lately been revived and further developed mainly by two authors. *Greaves* postulates an initial mutation in a B-precursor cell in-utero, where proliferation is high. One or more further mutation(s) then supposedly take place after birth under the influence of an infectious agent. These mutations are strongly dependant on the type of the agent and the moment of the influence [GRE 93a, GRE 97]. *Kinlen* proposes an aberrant response model in which an infection with some known ubiquitous virus takes place early in childhood or even in-utero and – as a very rare event – induces leukaemia. This is especially believed to be true for formerly secluded populations which now undergo population mixing [ALE 93, KIN 95, MAC 92].

Even less is known about the aetiology of chronic leukaemia. CLL shows a genetic component: there is a known familial risk as well as an increased risk in persons with trisomie 12 [WIE 01] and incidence among Asians is very low [FIN 92]. Studies concerning the influence of electromagnetic fields [FLO 93], benzene, pesticides and solvents remain contradictory [ZHE 02, ADA 99, RAA 96, FIN 92]. Only a viral aetiology is undisputed for certain types of chronic T-cell leukaemia which are known to be associated with HTLV I and possibly HTLV II [FIN 92].

For CML, there is a greater incidence in Blacks than in Whites, yet otherwise little evidence for a strong genetic component [FIN 92]. Benzene is widely accepted as a causative factor, but results in different studies are not entirely consistent [NOR 97, YIN 96]. The same applies to organic solvents and electromagnetic fields [BJO 01]. Similar to AML, there may be an increased risk of CML after chemotherapy, but further studies are required on this topic [BAU 02].

1.2. SITUATION AFTER THE CHERNOBYL NUCLEAR POWER PLANT ACCIDENT

The accident in the Chernobyl Nuclear Power Plant in Northern Ukraine that occurred on 26 April 1986 was the largest accident so far in the history of civil use of atomic energy. The accident and the subsequent fire in the reactor led to the release of large amounts of radioactive materials with an activity of 12 Exabecquerel (10^{18} Becquerel). Radionuclides such as ^{131}Iodine, ^{134}Caesium, ^{137}Caesium were dispersed over large parts of Europe depending on the wind and precipitation conditions. The most highly contaminated regions are in Belarus, the Western parts of Russia and the Northern Ukraine. The population in these regions is subject to persisting external exposure as well as internal exposure through radioactive foodstuffs. About 6.7 million people live in regions with levels of ground contamination with radiocaesium of 37 000 Bq/m² or more at the time of the accident, 1.4 million of which live in regions with levels of ground contamination of 185 000 Bq/m² or more, one fifth to one sixth are children under the age of 15.

There are two different kinds of exposure situations that need to be considered separately in the assessment of the long-term health effects of the Chernobyl accident:

The very large releases of short-lived radioiodine led to high doses in the thyroid gland. Prophylactic intake of stable iodine in the first days after the accident was not made available to the population in the immediately affected regions. Since the doses were accumulated in the first days and weeks after the accident, there was no possibility of subsequent remedial action. Consequently, a dramatic increase in thyroid carcinomas, especially in those who were children at the time, was later observed [RAR 99]. This is the one grave health effect directly due to the Chernobyl reactor accident.

Long-lived radioactivity, mainly from radiocaesium, led to continued low dose rate exposure of the inhabitants of the affected regions. This long-term exposure of large groups of the population was the major aspect that led to evacuations, restrictions in food production and consumption, and to general disruption. It remains an important issue in public health policy and public opinion. Persisting grave apprehensions are still focused on the continued exposure to radiation and on possible increases of cancer incidence, of hereditary defects and congenital malformations and – at least in the collective perception – even of general morbidity.

A lack of verifiable and comparable data and scientific publications makes the assessment of health effects in Belarus, Russia and the Ukraine due to the continued low radiation exposure after the Chernobyl accident very difficult. Particularly disastrous was the restrictive information policy of the Soviet government in the years following the accident: scarce and contradictory information led to misinformation and an overwhelming feeling of helplessness among the affected population who now tend to mistrust all information from official sources. To date, a distorted picture of real or supposed risks is often presented in the Western and Eastern press as well as in international scientific journals [e.g. PET 96 in *Nature*], which leads to further uncertainty: many of the affected persons now attribute any illness or unwellness to the radiation. The unresolved questions and remaining uncertainties have evoked continuous stress among the affected population and the resulting concerns and anxieties contributed to a deterioration in the living conditions and the quality of life in the affected regions. It is necessary to investigate further in order to provide reliable information as a basis for remedial action and effective counter-measures wherever these may be required.

1.3. STUDY FRAMEWORK AND TIMETABLE

In view of this situation, the German and French Ministers of the Environment, Angela Merkel and Corinne Lepage initiated the German-French Initiative for Chernobyl (GFI). The initiative comprises projects in the fields of

- safety of the sarcophagus
- radioecology
- health effects

The programme is being financed by the governments as well as by German and French electric power companies, Electricité de France (EDF) and Verband der Elektrizitätswerke (VDEW), with an overall budget of approximately 6 million Euro.

The main purpose of the GFI is to assist in the collection and validation of the existing data in the three most highly contaminated countries, Belarus, Russia and the Ukraine, to constitute a reliable and objective basis of information useful to the planning of countermeasures, for informing the public, and for future scientific work. In the health effects projects, the main aim is to obtain comparable data from the three countries using similar methodologies. It is essential that the data be of continuously high quality in order to allow a joint analysis. This will increase the power of the studies and thus the probability of obtaining reliable results.

The German Company for Plant and Reactor Safety (Gesellschaft für Reaktorsicherheit, GRS) is responsible for carrying out the GFI on the German side with the exception of the health effects projects – altogether eleven – which have been planned and implemented by the Radiobiological Institute of the University of Munich.

The data of the present thesis were obtained within the framework of subproject 3.2.4.: *Leukaemia Incidence Among Children and Adults in the Most Highly Contaminated Territories of Russia*, which started in April 1999 and ended as scheduled after three years in March 2002.

1.4. STUDY GOAL AND TECHNIQUE

The South-western parts of the Russian Federation, especially parts of the Bryansk and Kaluga oblasts, were contaminated due to the Chernobyl Nuclear Power Plant accident.

The objective of this study is to investigate whether there has been an increase in the incidence of leukaemia in the general population of these regions and whether and how such a possible increase may be linked to the radiation factor. To this end, a prospective cohort study with a control group was carried out for the years 1980 to 1998.

Cancer cases in the Soviet Union were registered in centralized, population-based cancer registries. The same applies to the Commonwealth of Independent States (CIS) from December 1991. The data that form the basis of this study were taken from the statistics departments of the oncological dispensaries of the Bryansk and Kaluga oblasts. They were ascertained, verified and validated together with the Radiobiological Institute of the University of Munich (LMU).

All cases of leukaemia that occurred between 1980 and 1998 in the affected regions of Russia (five rayons of the Bryansk oblast and 3 rayons of the Kaluga oblast) and the complete data from a neighbouring control region (3 rayons of the Kaluga oblast) - altogether 333 cases – are included in the analysis.

The main questions addressed in the present study are the following:

- are the data complete and of sufficiently high quality?
- is there a continuous documentation or an indication of an expectation or detection bias?
- what are the strengths and the limitations of the study?
- what are the estimated attributable risks of leukaemia in the study cohort and would these hypothetical cases be detectable against the fluctuation of the baseline cases?
- are the incidence rates in the population of the contaminated rayons similar to those of the populations in the control rayons?
- is there a secular trend in the incidence rates in the population of the contaminated rayons and, if so, are the rates after the accident considerably higher than before?
- are the results in line with the radiobiological experience or do they contradict the present risk co-efficients for radiation [UNS 94]?
- are the findings relevant in view of a public health approach and what do they imply?

2. MATERIALS AND METHODS

2.1. DEFINITION OF THE STUDY PERIOD

The study period was chosen to be 1980 – 1998, allowing a sufficiently realistic picture of the leukaemia incidence in the years before the accident to be achieved. It is further divided into three periods for various reasons:

Pooled time periods provide larger sample sizes and therefore higher power for the analysis of a possible secular trend. In view of this it is advantageous to divide the period in a way that produces approximately equal sample sizes.

Furthermore, both a possible expectation as well as a detection bias could be revealed only if a minimum of two consecutive post-accident periods were analysed. Both biases would lead to elevated incidence rates directly after the accident and a subsequent decrease. In the case of an expectation bias the incidence rates would simply return to the pre-accident level. In the case of a detection bias the rates would fall below the pre-accident rates after the initial increase before returning to the actual level.

Last, but not least, the time pattern of leukaemia occurrence after irradiation [SHI 95] proposes a division into an earlier and a later post-accident period: an increase in the incidence of leukaemia (excluding CLL) after irradiation can be observed after a latent period of about two years [PRE 94] with a peak of radiation-induced leukaemia occurring about five to eight years after irradiation [SHI 95].

Considering all of the above, it seemed suitable to choose the periods as follows:

- a pre-accident period (1980–1986)
- an early post-accident period (1987-1992)
- a late post-accident period (1993-1997)

2.2. RADIOLOGICAL SITUATION

2.2.1. CONTAMINATION

The Chernobyl Nuclear Power Plant accident on 26 April 1986 was the largest accident in the civil use of atomic energy. It led to the contamination of vast territories of Europe, especially of the former Soviet Union, and Scandinavia.

The contamination of Russia started on 28 April 1986 when north-easterly winds blew the radioactive cloud over from the Ukraine. Due to the intensive rainfalls (10 mm/h) over the boundary between the Mogilev and Gomel oblasts of Belarus and the Bryansk oblast of Russia on 28-29 April 1986 the large Bryansk-Belarus spot was formed. The rain washed out radionuclides from the radioactive cloud. This increased the speed of deposits of radionuclides on the soil leading to uneven, in some places high levels of contamination in the Bryansk and Kaluga oblasts.

The radioactive cloud remained over the south-western rayons of the Bryansk oblast for 13 hours from the afternoon of 28 April until 7 a.m. of 29 April 1986. It moved on to the east in the direction of Tula city and covered the territory of southern rayons of Kaluga oblast. The maximum level of radioactive contamination of the Tula-Kaluga-Oriol spot was lower by an order of magnitude compared to that of the Bryansk-Belarus spot. This is assumed to be due to an expansion of the cloud and its exhaustion after the previous deposits.

The level of exposure of the population of the three oblasts to radiation - especially in 1986 – was taken into account by the national and local authorities when decisions concerning radiation protection were made. These decisions were based on information from intensive radiation surveillance carried out from May 1986 by central and local bodies and institutions affiliated to the Goskomgidromet of the USSR (State Committee of Hydrometeorology of the USSR), the Ministry of Public Health of the Russian Federation and Gosagroprom (State Committee of Agricultural Industry).

Detailed maps based on the official data [MER 96] of the average density of ^{137}Cs contamination of the Bryansk and the Kaluga oblasts are given in figs. 2.1-2.2.

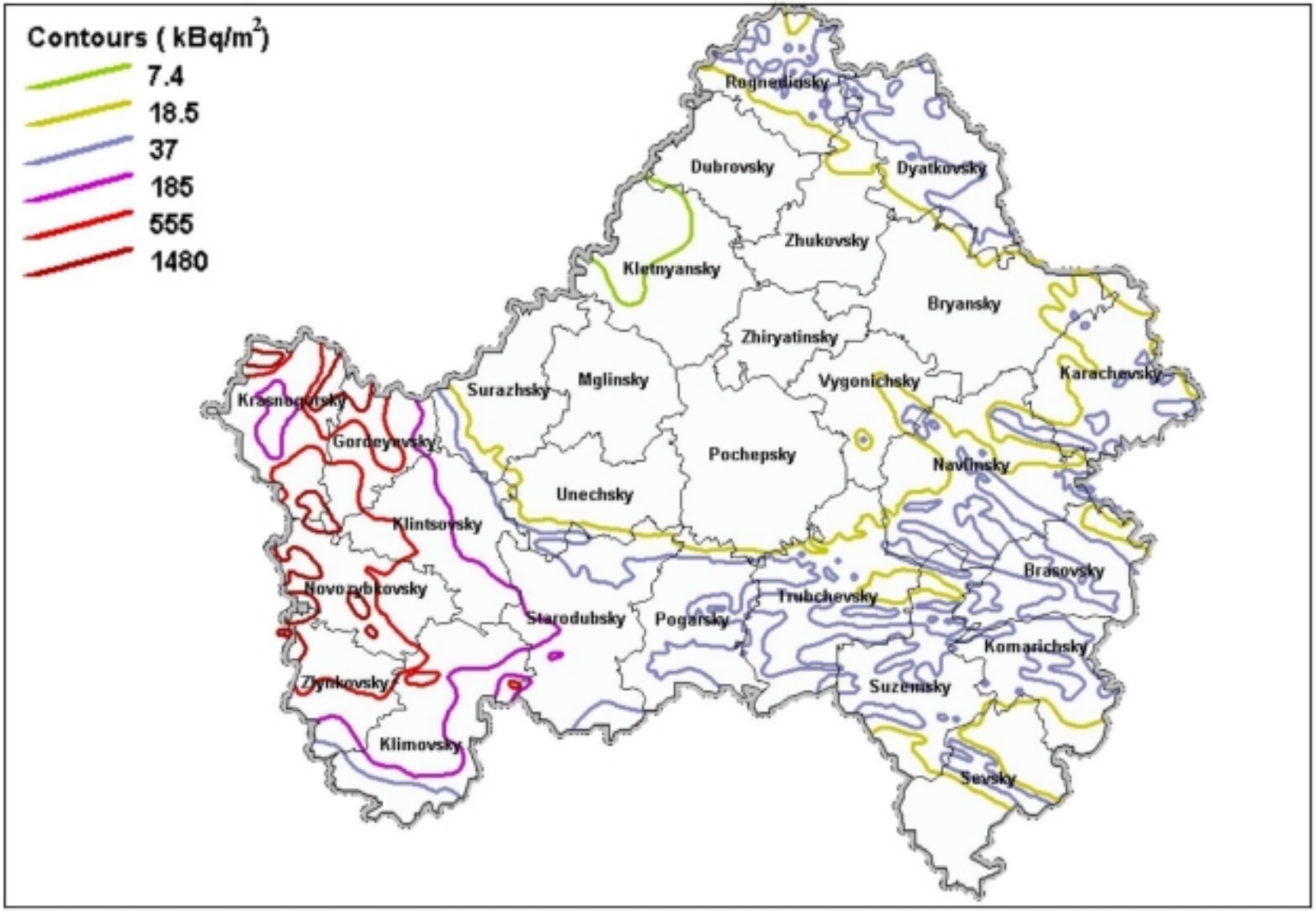


Fig 2.1 Official average density of ^{137}Cs contamination f the Bryansk oblast [MER 96]

Fig 2.2 Official average density of ^{137}Cs contamination in the Kaluga oblast [MER 96]

2.2.2. DOSES RECEIVED BY THE POPULATION

From the beginning of radioactive fall-out, the population was exposed externally and internally to a mixture of various products of fission and activation. Radioisotopes of iodine and caesium, as well as of strontium and plutonium, were the most significant contributors. Radiation monitoring was designed to estimate the density of soil contamination with long-lived radionuclides, such as ^{137}Cs, ^{90}Sr and isotopes of plutonium, in the settlements and surrounding territories; air concentration was measured as well. Radionuclide composition was studied, exposition dose rate from γ-radiation was measured, foodstuffs and water were tested for radionuclides, and whole body counts were performed. All this information allowed an estimation of the current annual doses to the population. However, it was very difficult to estimate radiation doses accumulated during the first year after the accident. At that time dozens of radionuclides with different radiological properties contributed to the dosimetry. The temporal changes of the radiation situation were rapid and depended on local environmental and social conditions.

Table 2.1 compiles some important characteristics of the radionuclides which reached the territory of the Russian Federation as a result of atmospheric transfer.

Table 2.1 Radionuclides deposited on the territory of Russia after the Chernobyl accident

Radionuclide				Period of half-life		Final stable isotope
Mother (m)	Type of radiation	Daughter (d)	Type of radiation	T_{mother}	$T_{daughter}$	
^{137}Cs	β	^{137m}Ba	β+γ	30.2 years	156 seconds	^{137}Ba
^{136}Cs	β+γ	–	–	13.1 days	–	^{136}Ba
^{134}Cs	β+γ	–	–	2.1 years	–	^{134}Ba
^{89}Sr	β	–	–	53.6 days	–	^{89}Y
^{90}Sr	β	^{90}Y	β+γ	28 years	64.3 hours	^{90}Zr
^{131}I	β+γ	–	–	8.0 days	–	^{131}Xe
^{132}Te	β+γ	^{132}I	β+γ	3.3 days	2.3 hours	^{132}Xe
^{133}I	β+γ	^{133}Xe	β+γ	0.9 days	5.3 days	^{133}Cs
^{140}Ba	β+γ	^{140}La	β+γ	12.7 days	1.7 days	^{140}Ce
^{95}Zr	β+γ	^{95}Nb	β+γ	64.0 days	35.2 days	^{95}Mo
^{103}Ru	β+γ	^{103m}Rh	β+γ	39.3 days	0.9 hours	^{103}Rh
^{106}Ru	β	^{106}Rh	β+γ	1.0 years	3 seconds	^{106}Pd
^{141}Ce	β+γ	–	–	32.5 days	–	^{141}Pr
^{143}Ce	β+γ	^{143}Pr	β+γ	1.4 days	13.6 days	^{143}Nd
^{144}Ce	β+γ	^{144}Pr	β+γ	0.8 years	0.3 hours	^{144}Nd
^{125}Sb	β+γ	^{125m}Te	β+γ	2.8 years	58.0 days	^{125}Te
^{99}Mo	β+γ	^{99m}Tc	β+γ	2.8 days	6.0 hours	^{99}Ru

Radionuclides with a half-life of less than one month decayed completely during the first year after the accident. Since the level of contamination of the soil with long-lived radioisotopes such as $^{95}Zr+^{95}Nb$, $^{106}Ru+^{106}Rh$, $^{144}Ce+^{144}Pr$ and ^{125}Sb was low, their contribution to the radiological situation after April 1987 is negligible.

For 5-7 years from April 1987, the main contributors to radioactive contamination of the territory were ^{137}Cs and ^{134}Cs. Whereas the contribution of ^{134}Cs to radioactive contamination decreased rapidly, the situation at present is determined by ^{137}Cs-contamination of the soil and environment (figs. 2.1 and 2.2).

To estimate radiation risks of leukaemia, effective doses both from internal and external exposure to the whole body should be accounted for. The procedure for estimation of the above doses was developed in Russia in 1996 by specialists of the Institute of Radiation Hygiene of the Ministry of Health of the Russian Federation (St.-Petersburg), the Medical Radiological Research Centre of the Russian Academy of Medical Sciences, the Institute of Biophysics of the State Research Centre of the Russian Federation, and the Scientific and Productive Association Taifoon of Rosgydromet. Their findings are documented as *Reconstruction of the Mean Effective Dose (accumulated for 1986-1995) to the Population of the Settlements of the Russian Federation Affected by Radioactive Contamination as a Result of the Accident at the Chernobyl NPP* [MER 96].

Based on these methodological recommendations, official data on the mean effective doses from external and internal exposure to the whole body of residents of the settlements of the Bryansk and Kaluga oblasts were estimated. The results of these estimations were discussed and adopted at the session of the Russian Scientific Commission on Radiation Protection in 1996.

About 90% of the total additional doses following the Chernobyl catastrophe were accumulated in the ten years from 1986 - 1995. The mean cumulative effective doses over 9.7 years were calculated for the population of 1 091 contaminated settlements (soil contamination over 37 kBq/m^2) of the Bryansk oblast and 404 contaminated settlements of the Kaluga oblast. Estimates of the mean cumulative doses received by the residents of these settlements in the Bryansk oblast are within the range of 4-167 mSv, for the residents of these settlements in the Kaluga oblast within the range of 1.4-25 mSv. The mean cumulative effective doses are given in table 2.2.

Table 2.2 Settlements of the Bryansk and the Kaluga oblasts with mean ^{137}Cs contamination density above 37 kBq/m^2 and the integrated mean cumulative effective dose (mSv) of internal and external exposure received by adults (1986 to December 31, 1995)

Range of the mean cumulative effective dose (mSv)		Number of settlements	Percentage (%)
Lower limit	Upper limit		
The entire Bryansk oblast : 1 091 settlements; mean cumulative effective dose 23.5 ± 19.2 mSv			
3	4	2	0.2
4	5	40	3.7
5	7	110	10.1
7	10	148	13.6
10	15	201	18.4
15	20	118	10.8
20	25	95	8.7
25	30	84	7.7
30	40	101	9.3
40	50	86	7.9
50	70	81	7.4
70	100	15	1.4
100	150	10	0.9
150	200	1	0.1
The entire Kaluga oblast: 404 settlements; mean cumulative effective dose 6.3 ± 4.9 mSv			
1	2	57	14.1
2	3	83	20.5
3	4	50	12.4
4	5	36	8.9
5	7	38	9.4
7	10	52	12.9
10	15	62	15.3
15	20	20	5.0
20	25	6	1.5

2.3. ESTABLISHMENT AND FEATURES OF THE STUDY COHORTS

Unfortunately for the purpose of this study, it was not possible to establish study cohorts on the basis of the population of settlements with similar contamination levels. This is due to the lack of reliable population data on the settlement level. It was thus necessary to resort to the rayon level, where sufficiently accurate population statistics can be obtained.

To establish the study cohorts, three groups of rayons were formed according to the prevailing levels of ground contamination:

highly contaminated: Gordeevsky, Zlynkovsky, Klintsovsky, Krasnogorsky, Novozybkovsky rayons of the Bryansk oblast;

slightly contaminated: Zhizdrinsky, Ulianovsky, Khvastovichsky rayons of the Kaluga oblast;

control: Baryatino, Babynino, Tarussa rayons of the Kaluga oblast.

The group of highly contaminated rayons includes the five most highly contaminated rayons of the Bryansk oblast, where the mean density of soil contamination with ^{137}Cs was higher

than 400 kBq/m^2 at the time of the accident. The group of slightly contaminated study rayons includes three rayons of the Kaluga oblast, where the mean density of soil contamination with ^{137}Cs was 90 - 200 kBq/m^2 at the time of the accident. Almost all rayons of the Bryansk and Kaluga oblasts are contaminated with radionuclides after the Chernobyl accident, but at substantially different levels. Three rayons of the Kaluga oblast which were contaminated with less than 25 kBq/m^2 at the time of the accident serve as control rayons.

2.3.1. DOSES RECEIVED BY THE STUDY COHORTS

The effective cumulative doses between 1986 and 1995 received by the study cohorts (highly contaminated, slightly contaminated and control) varies by more than two orders of magnitude. The actual doses are given in table 2.3.

Table 2.3 Cumulative effective doses and mean cumulative effective doses due to Chernobyl for 1986-1995 in the study cohorts

RAYONS	Mean cumulative effective dose (mSv) due to Chernobyl over 10 years (1986-1995)	Mean annual cumulative effective dose (mSv) due to Chernobyl during 1986-1995	Cumulative effective dose (person Sv) due to Chernobyl 1986-1995	Mean annual population (in 1 000) 1986-1995
Highly contaminated	22.9	2.29	5 098	222.6
Slightly contaminat.	7.4	0.74	343	46.2
Control	0.35	0.035	15	42.2

2.3.2. DEMOGRAPHIC FEATURES OF THE POPULATION IN THE STUDY AREAS

Demographic data on the age and sex structure of the population of the rayons under study were contributed by the Oblast Statistics Committee (Oblkomstat) on the basis of the censuses in 1979 and 1989. Table 2.4 gives the population at both censuses and in 1998.

Table 2.4 Population (in 1 000) in the three groups of rayons under study at the two censuses (1979 and 1989) and in 1998

RAYONS	1979	1989	1998	Difference 1979-1998 (in % of 1979)
Highly contaminated	243.4	227.7	208.7	- 14.3
Slightly contaminat.	57.4	42.4	38.7	- 32.6
Control	39.9	39.1	47.6	+ 19.3

The change in population size clearly exceeds the effect of a change in birth rate. This is also evident when assessing the demographic structure of the different populations (fig 2.3). The changes in the study regions must therefore be partly due to migration. Unfortunately, it is difficult to obtain detailed information on migration on the rayon level, especially where the

people might have migrated from or to [KOR 03]. Nevertheless, several aspects suggest that a possible migration effect would not strongly bias the overall results of this study.

Migration may be compulsory or chosen, even if it is an official resettlement of inhabitants of some highly contaminated areas by the local (oblast) authorities. The compulsory resettlement concerns only extremely highly contaminated areas and mostly happened fairly shortly after the accident, before high individual doses had been accumulated. Since any type of official resettlement took place within the same oblast or even within the same rayon, the population increase in the control rayons in the Kaluga oblast cannot be due to people officially resettled from the extremely highly contaminated areas in the Bryansk oblast. Due to much lower contamination, there was no compulsory resettlement at all in the Kaluga oblast. People migrating from the slightly contaminated study rayons (which are all located in the Kaluga oblast) to the control rayons in the Kaluga oblast might account for some of the population increase in the control rayons [KOR 03]. Their radiation risk, however, is so low (cf. 3.2.) that it is negligible in view of the remainder of the control cohort.

People may also migrate on their own accord for various reasons not directly linked to the radiation, i.e. for economic reasons or simply because they have family in other places, for example in Moscow [KOR 03]. These people would not necessarily be those with the highest risks. Since this type of migration would have occurred similarly in the highly contaminated and the slightly contaminated rayons, it would lead to non-differential misclassification.

For the above stated reasons, any migration might lead to a slight underestimation of the risk in the highly contaminated rayons in the worst case, but would not result in an overestimation of the risk in the control rayons.

Figure 2.3 illustrates that the sex and age structure of the three groups of rayons under study are comparable. The most striking feature is the dramatic decrease of the youngest age group (children 0-4years) between 1989 and 1998.

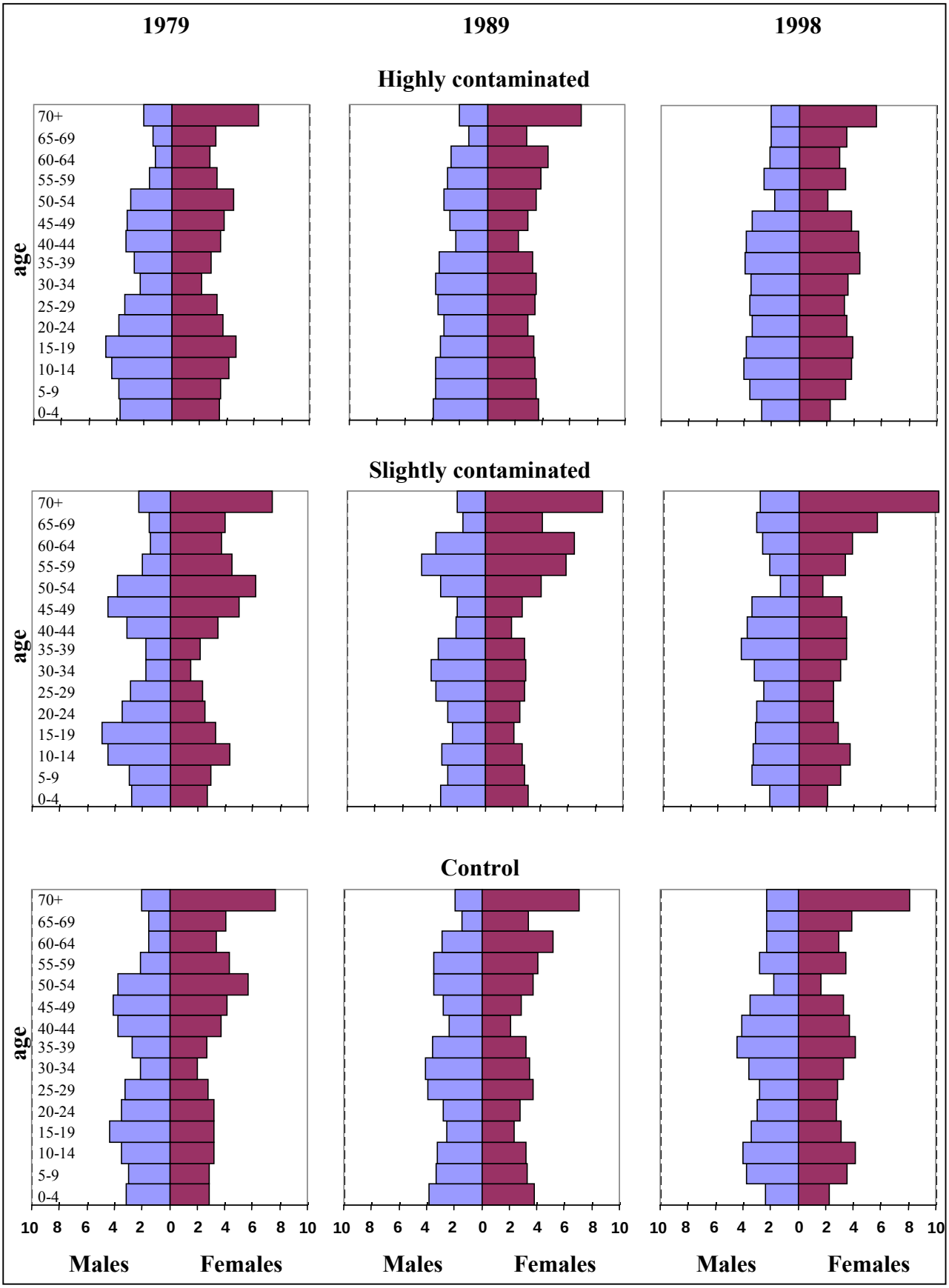


Fig 2.3 Demographic structure: share (%) of each 5-year age group in relation to the entire (male & female) population, the highest age group being 70+

2.4. TECHNIQUES OF ASCERTAINMENT AND VERIFICATION OF LEUKAEMIA CASES

The algorithm of the collection of leukaemia cases and of the verification of the diagnosis was elaborated by the staff of the *Russian Medical and Dosimetric Registry* in Obninsk. It is based on the cancer care and registration system of the former Soviet Union (fig 2.4).

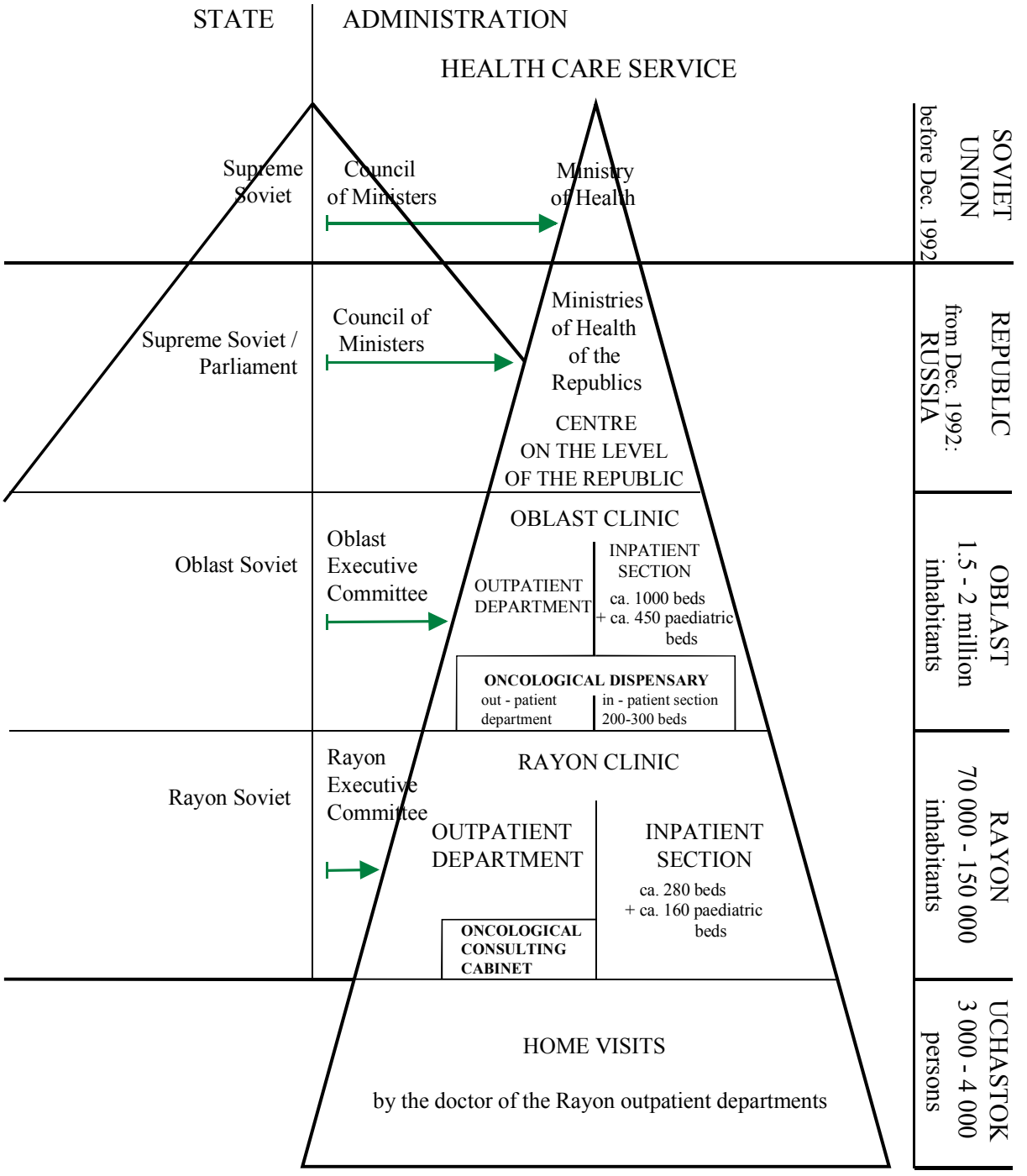


Fig 2.4 Cancer care and registration system of the former Soviet Union

The system of cancer care and registration that was in use in the former Soviet Union worked separately from the general health care system, but was structured analogously. The structure of this system has been conserved to the present day. The formation is strictly hierarchical, paralleling the administrative structures from the lowest level of the Uchastok - which exists only in the medical field – up to the level of the Republic. The resulting registries are population-based because the entire health care process is tied to the place of residence of the patient. The health care institutions are responsible for disease prevention and screening, diagnosis and therapy as well as for the registration of specific diseases.

The basic institution in which cancer patients are diagnosed and treated is the oblast oncological dispensary (OOD). Here all relevant medical and statistical information is stored in the archives.

The starting point of the collection and verification process thus is the OOD. Nevertheless, it sometimes involves medical institutions at the district level (in towns or in the country). This is due to some peculiarities of the leukaemia diagnosis, treatment and registration process in Russia, namely that the registration is covered by the OODs, whereas the diagnosis and treatment of leukaemia patients, as a rule, is performed in specialized haematological departments, possibly even in other oblasts than the patients‘ residence. Patients might thus not be in ‚their‘ population-based registry, so that the case has to be ascertained at the institution in question.

The routine documents for the diagnostic, therapeutic and registration process of solid cancers, leukaemia and lymphomas which are officially approved by the Ministry of Health are listed in tables 2.5 and 2.6. They form the basis for the collection of cases and the verification of diagnoses in this study. Table 2.5 gives the primary documents used in the Oblast Oncological Dispensary as well as in all in- and out-patient facilities. Further documents used in (specialized) medical institutions are given in table 2.6.

Table 2.5 Primary documents involved in the process of leukaemia registration

DOCUMENT TYPE	OFFICIAL FORM №	INSTITUTION	INFORMATION TRANSMITTED/ RECORDED
1. PRIMARY DOCUMENTS OF THE CANCER REGISTRATION PROCESS			
1.1 Notification of a cancer case diagnosed for the first time	090/u	all general and specialized in- and out-patients departments notify the cancer registry at the Oblast Oncological Dispensary (OOD)	notification of a newly diagnosed cancer case
1.2 Extract short extract from the medical history or the out-patient card	027-1/u	all medical institutions in which cancer is diagnosed and treated notify the cancer registry at the OOD	notification following diagnosis & treatment
1.3 Control Card control card for the follow-up of cancer patients at the oncological dispensary	030-5/u	the cancer registration department at the OOD	the Control Card is established when a new case is registered and is then regularly up-dated. Multiple primaries are registered on one Control Card. No Control Card exists for DCO-cases, Control Cards of deceased patients are removed from the database
1.4 Protocol	027-2/u	all institutions in which cancer is diagnosed; 2 copies: one copy for the OOD, the other remains in the archives of the issuing institution	reasons for late diagnosis in case of detection of a cancer case at an advanced stage
2. PRIMARY MEDICAL DOCUMENTS			
2.1 Out-patient Card medical card of the out-patient	025/u	all out-patient facilities	lifetime out-patient record
2.2 Medical History	003/u	all in-patient facilities	medical history for each single admission
2.3 Epicrisis detailed extract from the medical history	027-2/u	all in-patient facilities	summary of diagnosis & treatment
3. ADMINISTRATIVE DOCUMENTS			
3.1 Certificate of death	106/u	all medical doctors, for submission to the vital statistics departments (ZAGS)	date, cause and place of death as well as the place of official registration

Table 2.6 Other documents consulted in the ascertainment and verification process

DOCUMENT TYPE	INSTITUTION	INFORMATION RECORDED
1. DOCUMENTS OF CANCER REGISTRATION		
1.5 Electronic cancer registry	OOD	name, first name, year of birth, address, diagnosis, date of registration
1.6 List of initially diagnosed cancer patients	OOD	name, first name, year of birth, address, diagnosis, date of registration
1.7 Journal of initially diagnosed cancer patients	Oncological Cabinet at the Central Rayon Clinic	name, first name, year of birth, address, diagnosis, date of registration
1.8 Journal of deaths of cancer patients	Oncological Cabinet at the Central Rayon Clinic	name, first name, year of birth , address, diagnosis, date of death
2. MEDICAL DOCUMENTS		
2.4 Journal of myelograms & cytochemical analyses	Clinical – Diagnostic Laboratories of the Oblast Clinic (OC) & the Paediatric Oblast Clinic (POC)	name, first name, department, date and results of the analysis
2.5 Journal of biopsies of bone marrow or lymphatic nodes	Patho-Anatomical Laboratory of the OC & the POC	name, first name, department, date and results of the analysis
2.6 Medical comment	consulting out-patient departments	diagnosis, state at the moment of consultation, recommended therapy of the consulting haematologist
2.7 Protocol of autopsy	Patho-Anatomical Laboratory of the OC & the POC	name, first name, department, date and result of the autopsy

This entire complex of accessible documents in the various medical institutions from the rayon to the oblast level allowed a complete collection of possible information on the leukaemia cases. The algorithm that was followed in the data collection is given in table 2.7.

Details of the collection and verification of leukaemia cases are described in the annexe. In the process of the quality assessment of the data pertaining to every case the information was recorded in a special form, the *Verification Card of the Leukaemia Patient* (Annexe 2, figure A2.1).

Table 2.7 Process of ascertainment and verification of leukaemia cases

TASKS	SOURCES OF INFORMATION
STAGE I Oblast Oncological Dispensary	
Comparison of data entered into the database with primary data for the following items: 1) correctness and completeness of diagnosis 2) verification of dates 3) agreement between clinical and histological diagnosis Search for cases absent in the database (db) Elimination of unconfirmed cases from the database	Notification of cancer cases (1.1)* Extract from medical history (1.2)* Control card (1.3)* Electronic database of the OOD (1.5)* Journal of deceased cancer patients (1.7)* Out-patient Card (2.1)*
STAGE II Oblast Clinic Paediatric Oblast Clinic Archives and Registration Office	
Verification of recorded diagnoses Search for new cases Elimination of unconfirmed diagnoses	Out-patient Card (2.1)* Medical History (2.2)* Epicrisis (2.3)* Histological Archives of the Clinical-Diagnostic and Patho-Anatomical laboratory at the OC & POC (2.4, 2.5, 2.6)*
STAGE III Central Rayon Clinic Archives and Registration Office	
Comparison of data entered into the database of the oncological dispensary with primary data from the rayon Verification of recorded diagnosis *leukaemia* Search for cases absent in the database Elimination of unconfirmed diagnoses	Out-patient Card (2.1.)* Medical History (2.2.)* Journal of the Oncological Cabinet (1.7, 1.8)* Archive of the ZAGS (3.1)*

* the figures in brackets refer to tables 2.5 and 2.6.

2.5. RESULTS OF ASCERTAINMENT AND VERIFICATION

As a result of the consultation of the official and local registration and medical documents, patients formerly not registered were taken into account. At the same time, cases had to be excluded from the analysis because the diagnosis could not be confirmed. These movements in the primary database and the finally resulting database are documented in table 2.8.

2.5.1. REGIONAL DIFFERENCES

The results of the ascertainment and verification of leukaemia cases in the different study regions is presented in table 2.8.

Table 2.8 Results of ascertainment and verification of leukaemia cases in the different study regions

GROUPS OF RAYONS UNDER STUDY	CASES						
	OOD Data-base	Ascertainment		Interim total	Verification		Final Project Database
		Added			Excluded		
		No	%		No	%	
Highly contaminated	255	12	4.7	267	20	7.5	247
Slightly contaminat.	41	6	14.6	47	2	4.2	45
Control	35	18	51.4	53	12	22.6	41
TOTAL	**331**	36	10.9	**367**	34	9.3	**333**

331 leukaemia cases had been registered in the original database at the oblast oncological dispensary for the study rayons during the years 1980 – 1998. On scrutinizing the documents of other haematological disorders and cancers as well as of institutions other than those located directly in the study areas, 36 validated cases were added (10.9% of the cases originally registered at the OODs). It should be pointed out that the highest percentage of cases revealed through active registration during this project in relation to the originally registered cases in the database of the Oblast Oncological Dispensary occurred in the control rayons.

The further verification of diagnoses led to the exclusion of 34 cases (9.3% of the new total), leaving 333 cases in the final analysis.

2.5.2. SOURCES OF AND GROUNDS FOR INCLUSION AND REASONS FOR EXCLUSION OF CASES

A detailed description of the sources of the cases added to the database after case ascertainment and the grounds for their inclusion are given in table 2.9.

Table 2.9 Sources of and grounds for inclusion of leukaemia cases in the database

TOTAL OF CASES INCLUDED	CASES	
	No	%
	36	**100**
Source and grounds for inclusion		
OOD	**21**	**58.4**
date of diagnosis changed	4	11.1
discovered in other than the study rayons	2	5.6
revealed in the archives of out-patient cards	10	27.8
revealed in the main electronic database of all tumours with:	5	13.9
stomach cancer	2	
lymphoma	2	
lymphomatoid granulomatosis	1	
Oblast Clinic	**11**	**30.6**
haematological department		
Clinical-Diagnostic Laboratory	**2**	**5.5**
journal of myelograms (2.4)*		
Oncological Cabinet at the Central Rayon Clinic	**2**	**5.5**
journal of initially diagnosed cancer patients (1.7)*		

* the figures in brackets refer to tables 2.5 and 2.6

Nearly 60% of the 36 cases added to the database were discovered in Oblast Oncological Dispensaries – either of the study regions or, in two cases, of neighbouring oblasts. Ten cases of those that were found in the study area had simply not been reported earlier, but were diagnosed and registered correctly in the out-patient cards, whereas nine cases had not been included in the database for faulty information: in four cases the date of diagnosis was incorrect, and in five cases the diagnosis itself proved to be wrong.

Over 40% (fifteen cases) had not been registered at the Oblast Oncological Dispensary at all. They were discovered by searching medical records and archives of other general and specialized medical institutions of the oblast.

An overview of the results of case ascertainment and data verification together with the reasons for the exclusion of cases is presented in table 2.10.

Table 2.10 Results of case ascertainment and data verification together with reasons for the exclusion of cases

	CHANGES IN THE DATABASE	CASES	
		No	%
ASCERTAIN-MENT	**Number of cases in the database of the OOD**	**331**	**100**
	Added cases	36	10,9
	Total	**367**	**100**
VERIFICATION	Rejected:	34	9.3
	due to mistakes of diagnosis	25	6.8
	due to technical errors (wrong address, duplication of data, diagnosis established before 1980 or after 1998)	9	2.4
	Accepted cases	**333**	**100**
	Quality of data improved:	219	65.8
	type of leukaemia recorded more precisely	84	25.2
	date of birth recorded more precisely	65	19.5
	date of diagnosis recorded more precisely	70	21.0

The database resulting after the inclusion of the 36 cases stated in table 2.9 consisted of 367 cases. Each case was carefully verified which led to the subsequent exclusion of 34 cases. Obviously it was not possible to verify all information in the database - neither for all areas under study nor for all times, especially not for the earlier years for which parts of the documents are not in the archives. The same applies to the bone marrow smears, which have a limited conservation period of five years. A detailed description of the various reasons for exclusion is presented in table 2.11.

Table 2.11 Reasons for exclusion of leukaemia cases due to mistakes

TOTAL NUMBER OF CASES EXCLUDED		CASES	
		No	%
		34	**100**
due to wrong diagnoses		**25**	**73.5**
Diagnosis in the database	Correct diagnosis		
Chronic lympholeukaemia (204.1)	Non-Hodgkin's lymphoma (200.1) Multiple myeloma (203.0) Lymphogranulomatosis (201)	8 7 1	47.1
Chronic erythroleukaemia (207.1)	Symptomatic erythraemia (289.0)	1	2.9
Chronic leukaemia (208.1)	Aplastic anaemia (284)	1	2.9
Acute leukaemia (208.0)	Anaemia of uncertain aetiology (285.0) Megaloblastic anaemia (281.0) Death before diagnosis, no autopsy (798.2)	3 1 2	17.7
Leukaemia (208.9)	Lymphatic node metastasis (196.9)	1	2.9
due to technical errors		**9**	**26.5**
Wrong address		3	8.8
Duplication of data		2	6.0
Diagnosis already established in a region not included in the study		1	2.9
Diagnosis established before 1980 or after 1998		3	8.8

Most (73.5%) of the cases that had to be excluded from the database had to be discarded due to wrong diagnoses. The most problematic diagnoses were chronic leukaemia, especially CLL, half of which (8 cases) had been misdiagnosed as Non-Hodgkin's lymphoma. Seven alleged cases of CLL were in fact multiple myeloma but had been miscoded by the technician at the cancer registry.

A detailed description of the verification of diagnoses at all stages is included in Annexe 2.

2.6. TYPE OF STUDY AND STATISTICAL METHODS

The study is designed as a prospective population-based cohort study with a control group ('prospective' in that the exposure – in this case the ground contamination – is measured before the disease onset). In view of the negligible radiation risks of the cohort from the slightly contaminated rayons (cf. 3.2), these study rayons are pooled with the control rayons for the analysis to form the combined control rayons (CCR) and thus increase the power of the study.

A descriptive analysis is performed on all the cases:

In a regional analysis, the absolute number of cases as well as the crude and age- and sex-standardized (world standard) rates in the highly contaminated rayons (HCR) are compared to those of the combined control rayons (CCR). 95% Confidence Intervals according to Poisson are given for the crude rates and the χ^2-test is performed to test for homogeneity of the standardized rates. Age-specific rates over the entire study period are given for the contaminated and the control rayons together with 95% Confidence Intervals according to Poisson.

In a temporal analysis, three study periods (cf. 2.1) are introduced. The resulting increase in power then allows a separate analysis for children (0-14 years) and adults, in which the standardized incidence rates for the three study periods in the contaminated and the control rayons are compared.

When discussing the possibility of detecting a radiation effect in the study rayons, 95% confidence intervals are given for the 703 cases expected in the study cohort over the entire lifetime. They are calculated on the basis of a standard distribution which provides a good approximation of the Poisson distribution for larger numbers.

3. RESULTS

All cases that occurred in the study areas between 1980 and 1998 – altogether 333 - were taken into the analysis.

3.1. ANALYSIS OF DATA QUALITY

3.1.1. DISTRIBUTION OF CASES BY PERIOD

Table 3.1 shows the distribution of the cases by region and three time periods.

Table 3.1 Distribution of cases by period

RAYONS	1980-98		1980-86		1987-92		1993-98	
	No	%	No	%	No	%	No	%
Highly cont.	**247**	100	79	32,0	77	31,2	91	36,8
Slightly cont.	**45**	100	14	31,1	6	13,3	25	55,6
Control	**41**	100	11	26,8	13	31,7	17	41,5
Total	**333**		**104**		**96**		**133**	

The cases are evenly distributed only in the highly contaminated rayons. There is an increase in the slightly contaminated and control rayons between the second and the third period by a factor of 2.2 for both types of rayons together. Interestingly this reflects roughly the magnitude of the actual increase in these rayons (cf. the standardized incidence rates, chapter 3.5, fig 3.6). Furthermore, it is improbable that an increase in reporting due to elevated awareness after the Chernobyl accident should occur between the second and the third period. Such an increase, if any, would have been expected in the second period in comparison to the pre-accident period (cf. chapter 2.5.1, table 2.8).

3.1.2. DISTRIBUTION OF CASES BY AGE

The distribution of cases by age in the different regions is given in table 3.2.

Table 3.2 Distribution of cases by age

RAYONS	1980-98		1980-86		1987-92		1993-98	
	age 0-14	age 15+	age 0-14	age 15+	age 0-14	age 15+	age 0-14	age 15+
Highly cont.	27	220	14	65	5	72	8	83
Slightly cont.	3	42	1	13	0	6	2	23
Control	5	36	0	11	4	9	1	16
Total	**35**	**298**	**15**	**89**	**9**	**87**	**11**	**122**

Over the entire period and in all the cohorts, 10.5% of the cases occurred in children (0-14 years), 89.5% in adolescents and adults. Due to the very small number of cases in children in the separate cells, a large variation of the corresponding percentages can be expected. The variation diminishes when looking at the different study cohorts over the entire period. The overall pattern is similar to that in other countries [CIN 92, 97]. However, the study rayons are rural areas and it cannot be ruled out that there is an underdetection (rather than an underregistration!) in the elder age groups. If anything, such a possible underdetection might be expected to increase with the deterioration of the public health care system in the 1990s. It must be emphasised that there is no indication of this being a major problem in this study.

3.1.3 DISTRIBUTION OF CASES BY DIAGNOSIS

The pattern of the different types of leukaemia in the study and control regions in the different periods is demonstrated in figs. 3.1 – 3.3. The corresponding data are given in tables A2.2-A2.5 in ANNEXE 2.

The distribution of leukaemia subtypes shows similar patterns regardless of the period, but the share of *leukaemia not otherwise specified* (ICD 9 208.0, 208.1, 208.9) decreases in the later years.

In children (fig. 3.1), most cases are acute lymphoblast leukaemia, as is typical in the remainder of Russia and the World [ALE 88, CIN 97]. Unfortunately no prevalence of different phenotypes or the Philadelphia chromosome (Ph+ or Ph-) in acute lymphoid leukaemia can be given because cytogenetic analysis is scarcely performed. It may be assumed that some of the more aggressive cases were Ph+ as this phenotype is known to be especially resistant to therapy [SCH 98, UCK 99]. One of the 35 cases detected in children was found to be chronic myeloid leukaemia in an eight-year-old boy. CML is an extremely rare disease in children; nevertheless, in this case the diagnosis was undoubtedly correct [FRE 98]. As the atypically high percentage (2.86%) of CML in children in the study regions is due to only this one case it can clearly not be seen as an overdispersion.

In adults (fig 3.2), the pattern of distribution of different leukaemia subtypes is typical of all periods of the study and conforms to the pattern in the remainder of Russia and the World [CIN 97]. 38.8% of all cases in adults were acute leukaemia, 55.2% chronic forms. In 6% of the cases, the form could not be established retrospectively.

The distribution of the different cytological types of leukaemia depends on the age (figs. 3.1, 3.2, ANNEXE 2 table A2.2-A2.3). Neither the distribution of the acute nor of the chronic forms (ANNEXE 2 table A2.5) differ from Russian and international data of the recent years [CIN 97]. Most (85%) of the cases of acute leukaemia in children were lymphoid leukaemia, in adults their share was 37.8% of the acute forms. Among the cases of chronic leukaemia in adults, CML accounted for 34% and CLL for 56%, which is totally in line with international experience [FAJ 80, SCH 93, KRO 95].

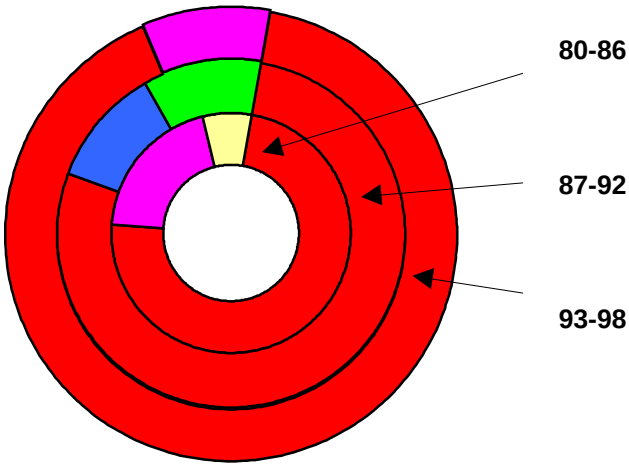


Fig 3.1 Different forms of leukaemia in children in the three time periods

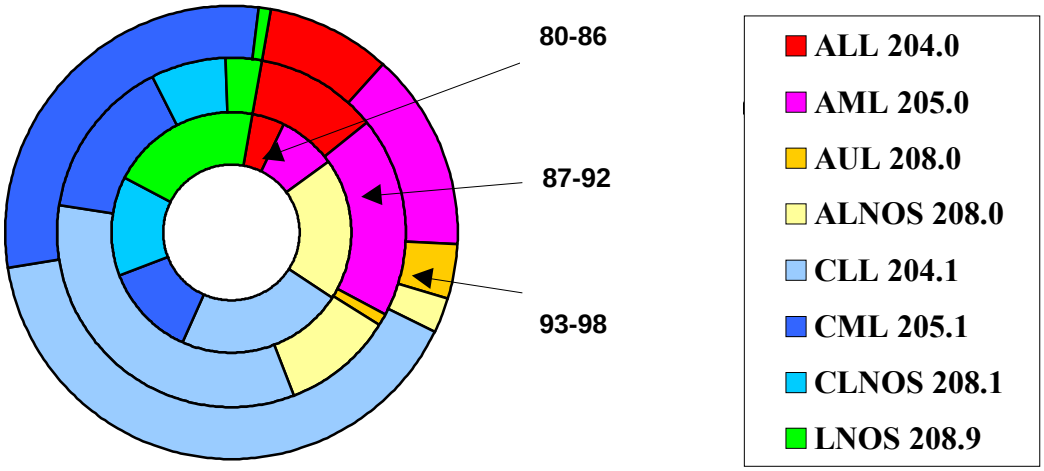


Fig 3.2 Different forms of leukaemia in adults in the three time periods

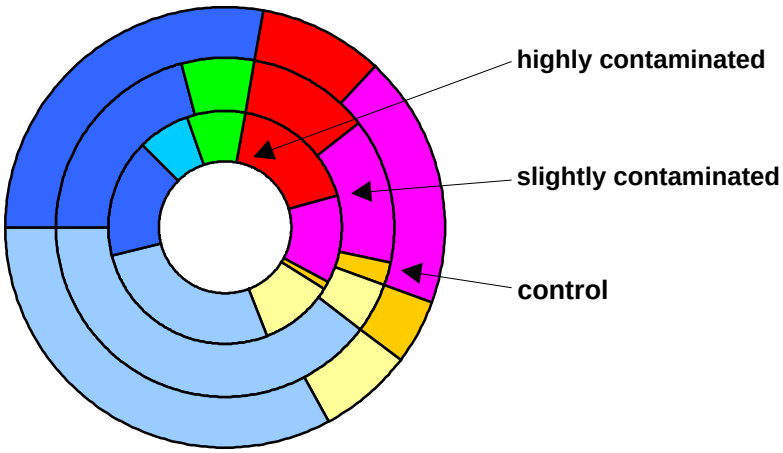


Fig 3.3 Different forms of leukaemia in the different rayons under study in 1980-1998

In recent years scientists came up with the idea that some forms of CLL might be inducible by radiation, especially leukaemia stemming from large granular lymphocytes of the phenotype of natural killer cells [GLU 01, IMA 01, LAM 98, LOU 98, IMA 90]. Unfortunately no cases with cells typed as large granulating cells or as natural killer cells were found. Although these cells may be identified by morphological criteria from routinely stained smears, this information is not available from most Rayon or even Oblast Clinics.

The only aspect that draws attention is the fact that the cases of chronic leukaemia are nearly evenly distributed among CML and CLL in the contaminated rayons of the Kaluga oblast whereas usually the incidence of CLL in Russia is 1.5-3 times higher than that of CML. So far there is no explanation for this overdispersion of CML.

All in all, there is no indication of poor data quality in respect of the diagnostic accuracy after the verification of diagnoses in the framework of this study.

3.2. CUMULATIVE ATTRIBUTABLE RISKS OF LEUKAEMIA

The attributable risk indicates the percentage of the cases that may be attributed to the influence of a certain causative factor during a defined time period. The cumulative attributable risks of leukaemia due to the radiation after the Chernobyl accident among the population of the contaminated rayons of the Bryansk and Kaluga oblasts are given in table 3.3. The cumulative risks were calculated using the prognostic UNSCEAR-model [UNS 94] for the time after the latent period, beginning from 1989**.** The total life-expectancy was assumed to be 90 years.

Table 3.3 Estimation of cumulative attributable risks of leukaemia [KAI 02]

AFFECTED RAYONS	CUMULATIVE ATTRIBUTABLE RISKS OF LEUKAEMIA (ENTIRE POPULATION)					
	1989-1994			lifetime expected		
	calculated baseline (cases)	radiation-related (cases)	attributable (%)	baseline (cases)	radiation-related (cases)	attributable (%)
Gordeevsky	4.40	0.78	15.1	48.3	2.07	4.1
Zlynkovsky	4.49	0.91	16.9	50.5	2.46	4.6
Klintsovsky	32.1	2.42	7.0	344.0	6.21	1.8
Krasnogorsky	6.01	1.68	21.8	64.2	4.32	6.3
Novozybkovsky	18.49	3.45	15.7	196.5	8.86	4.3
Highly contaminated	**65.49**	**9.24**	12.4	**703.5**	**23.92**	3.3
Zhizdrinsky	4.25	0.17	3.8	49.2	0.46	0.9
Ulianovsky	3.41	0.2	5.5	41.9	0.59	1.4
Khvastovichsky	5.07	0.25	4.7	56.4	0.68	1.2
Slightly contaminated	**12.73**	**0.62**	4.6	**147.5**	**1.73**	1.2

The radiation-related attributable risks of leukaemia for the years from 1989 to 1994 are 12.4% in the highly contaminated rayons and 4.6% in the slightly contaminated rayons. As the radiation-induced risk of leukaemia decreases with time following the exposure, the lifetime attributable risk is approximately 3 to 4 times lower than the attributable risk for the period 1989-1994. Estimates show that about 75% of all radiation-induced lifetime cases would occur within the 15 years after the latent period, i.e. between 1989 and 2003.

3.3. ANNUAL NUMBER OF CASES AND STANDARDIZED INCIDENCE RATES – A REGIONAL COMPARISON

The cumulative attributable risk in the population of the three contaminated Kaluga rayons is very small (table 3.3). For further analysis, these three rayons will be combined with the three control rayons of the Kaluga oblast. They will thus form a larger control group (combined control rayons, CCR) for a powerful statistical analysis in relation to the Bryansk study rayons (highly contaminated rayons, HCR).

To date, it has not been proved that CLL is induced by radiation. The following analyses were therefore performed both for all leukaemia and for all leukaemia excluding CLL.

The number of leukaemia cases between 1980 and 1998 among males and females for all leukaemia and for all leukaemia excluding CLL are presented in fig 3.4 for the highly contaminated (a-b) and the combined control rayons (c-d). The mean annual number of all leukaemia in the highly contaminated rayons is 13, ranging from 6-20; in the combined control rayons it is 4.53, ranging from 0-11. This difference in annual incidence is not significant when considering the difference in population size and age and sex structure, as can be seen from the standardized incidence rates.

Leukaemia incidence rates differ in the various age groups and between the sexes. This implies that the age and sex distribution in a population influences the crude incidence rates. In order to assess the incidence rates of different times and regions it is thus necessary to adjust for the composition of the population, i.e. to directly standardize the rates in order to make them comparable.

Crude and standardized (world standard) incidence rates per 100 000 persons between 1980 and 1998 are given in fig 3.5 for the highly contaminated rayons and in fig 3.6 for the combined control rayons. The rates for all leukaemia (a-b) and for all leukaemia excluding CLL (c-d) are given for males and females separately. The crude rates are given separately with the corresponding 95%-CI's; no significant fluctuations is observed between the years. The regression line indicates the trend of the standardized rates over the entire period.

It is remarkable that the standardized rates are rather instable in their relation to the crude rates and this might lead one to assume that the population in the study areas is extremely unstable from one year to the next. This is, however, not the case. The effect is due to the small number of cases in each year and the fact that they are distributed very inhomogenously between the various age-groups.

The mean morbidity in males in the contaminated rayons (all leukaemia: 6.2/100 000 [95%CI 5.1; 7.4] per year, all leukaemia excluding CLL: 4.2/100 000 [95%CI 3.3; 5.2] per year) is comparable to that in females in the contaminated rayons (all leukaemia: 5.8/100 000 [95%CI 4.9; 6.9] per year, all leukaemia excluding CLL: 4.5/100 000 [95%CI 3.7; 5.5] per year, the difference being non-significant: p-value of two-sample test for binomial proportions [BIN 02] 0.61 and 0.70 respectively). The same is true for the combined control rayons (all leukaemia among males: 5.4/100 000 [95%CI 3.9; 7.4] per year, all leukaemia excluding CLL: 3.3/100 000 [95%CI 2.1; 4.9] per year; all leukaemia among females: 5.1/100 000 [95%CI 3.7; 6.7] per year, all leukaemia excluding CLL among females: 3.4/100 000 [95%CI 2.3; 4.9] per year, the difference being non-significant: p-value of two-sample test for binomial proportions 0.74 and 0.87 respectively).

The leukaemia rates and their secular trends are comparable in the highly contaminated rayons and in the combined control rayons: there is a very small increase over time and this is slightly more marked among females than among males both for all leukaemia excluding CLL and for CLL alone.

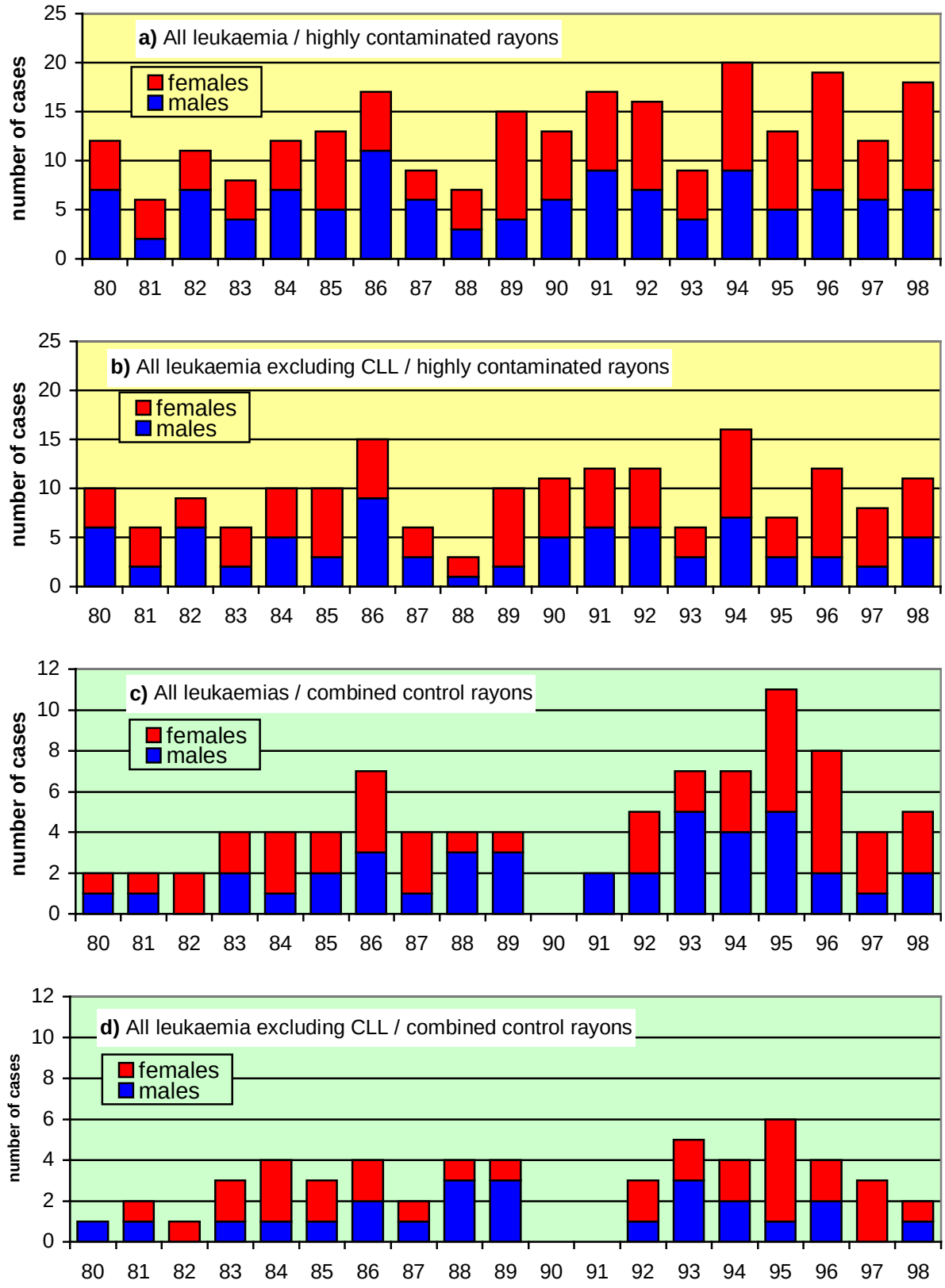


Fig 3.4 Leukaemia cases over the entire study period (1980-1998)

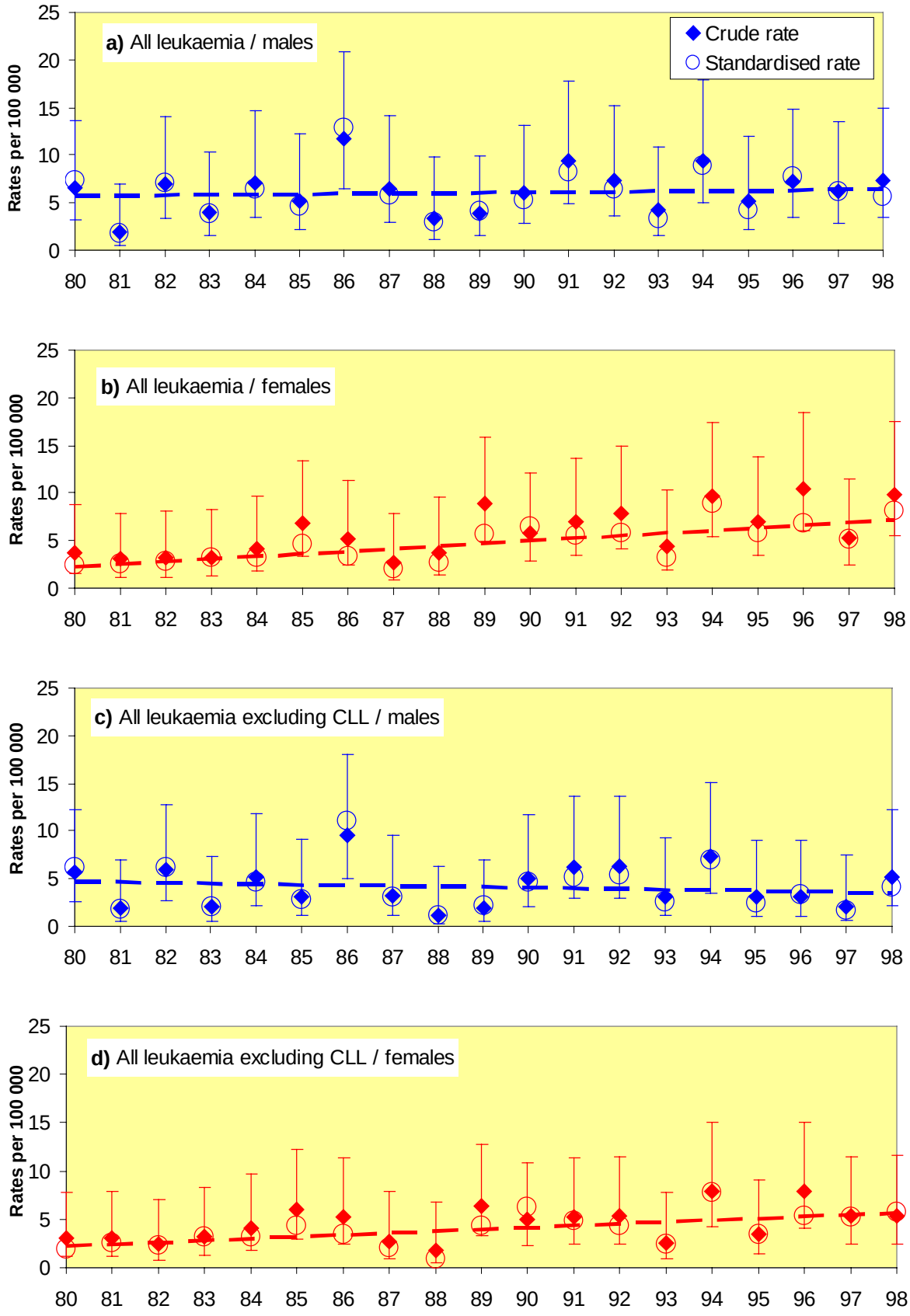


Fig 3.5 Crude and standardized (world standard) incidence rates (per 100 000) in the highly contaminated rayons. Vertical bars indicate 95% CI's for the crude rates according to Poisson; the regression line is calculated for the standardized rates

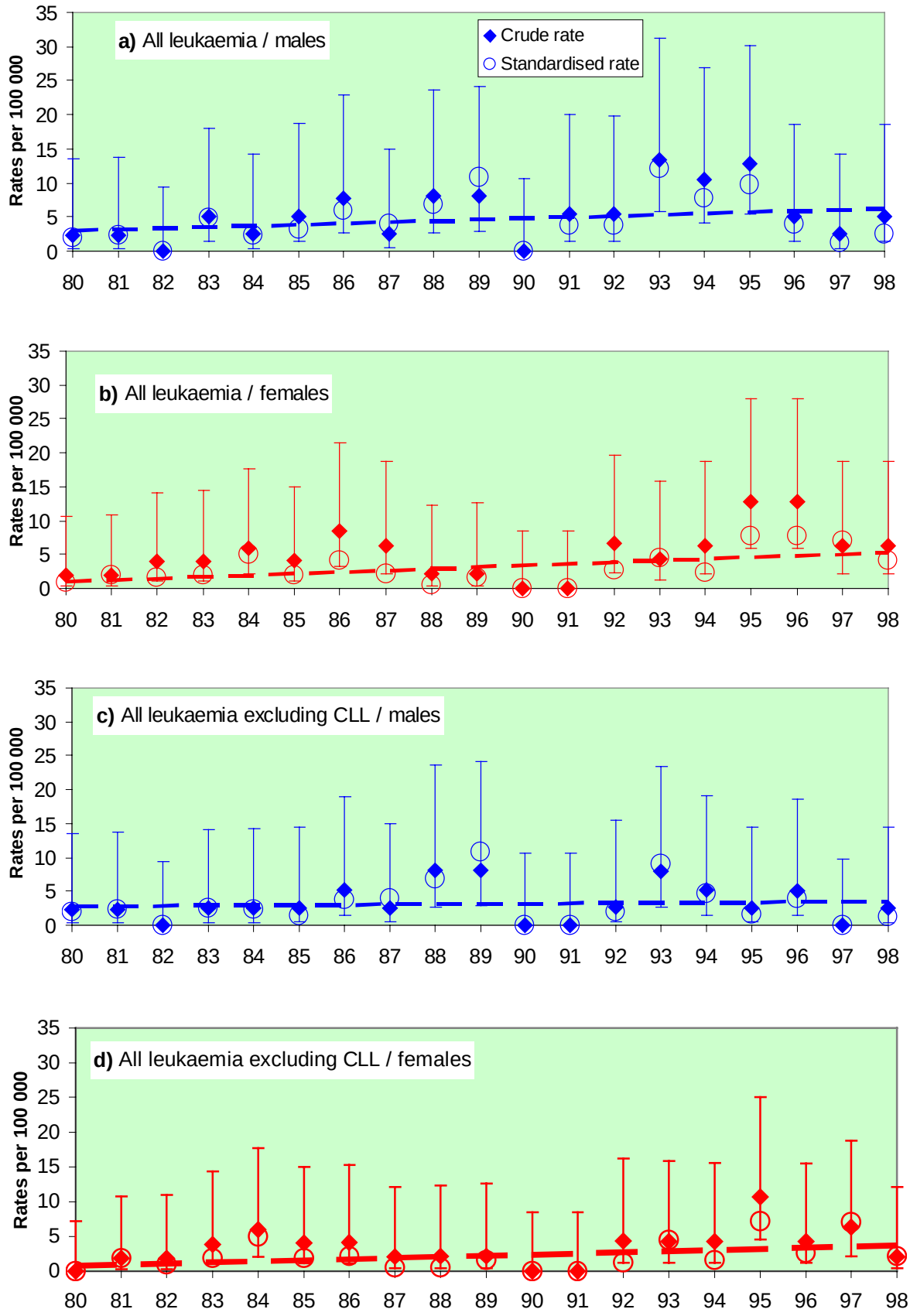


Fig 3.6 Crude and standardized (world standard) incidence rates (per 100 000) in the combined control rayons. Vertical bars indicate 95% CI's for the crude rates according to Poisson; the regression line is calculated for the standardized rates

3.4. STANDARDIZED INCIDENCE RATES – A TEMPORAL COMPARISON

In fig 3.7, the standardized (world standard) incidence rates are given for each of the three periods for all leukaemia and for all leukaemia excluding CLL. A comparison of the standardized rates for adults in the highly contaminated and the combined control rayons shows – both for all leukaemia and for all leukaemia excluding CLL - that the incidence rates are higher in the highly contaminated rayons in the earlier periods. There is a slight increase in incidence rates for both groups of rayons mainly in the third period. However, this increase is more marked in the combined control rayons, so that the incidence rates for the third period are similar in the combined control rayons and in the highly contaminated rayons.

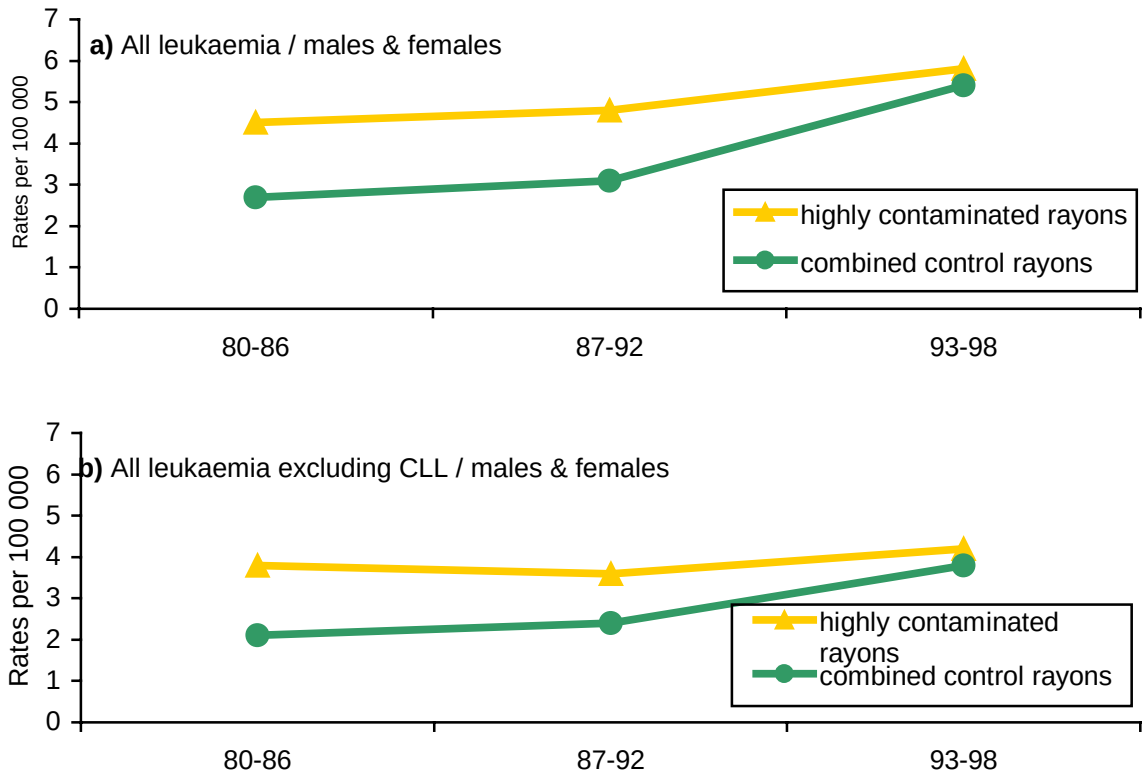


Fig 3.7 Standardized (world standard) leukaemia incidence rates (per 100 000) over the three study periods

The standardized leukaemia incidence rates for children (0-14 years) shown in fig 3.8 are substantially higher in the highly contaminated rayons in the pre-accident period, but drop below the rates of the combined control rayons in the early and the later post-accident period - the rates in the later post accident period are practically identical. This effect is due both to a decrease in the rates in the contaminated rayons and an increase in the rates in the combined control rayons.

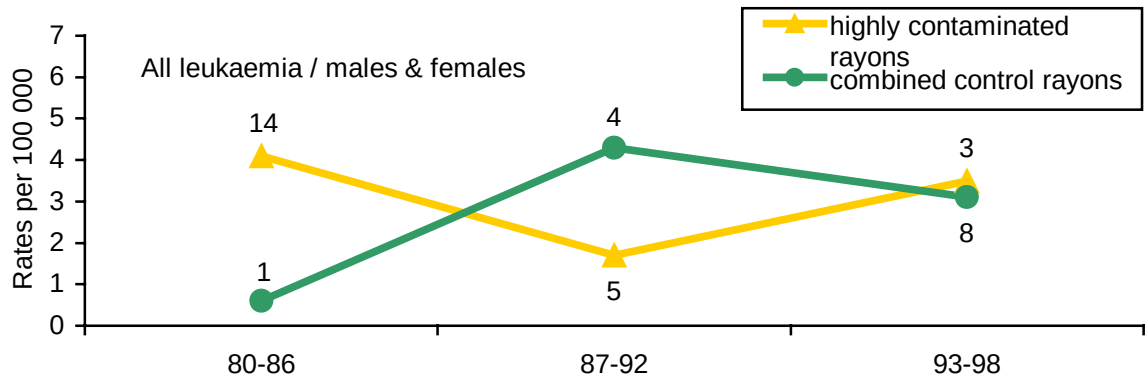


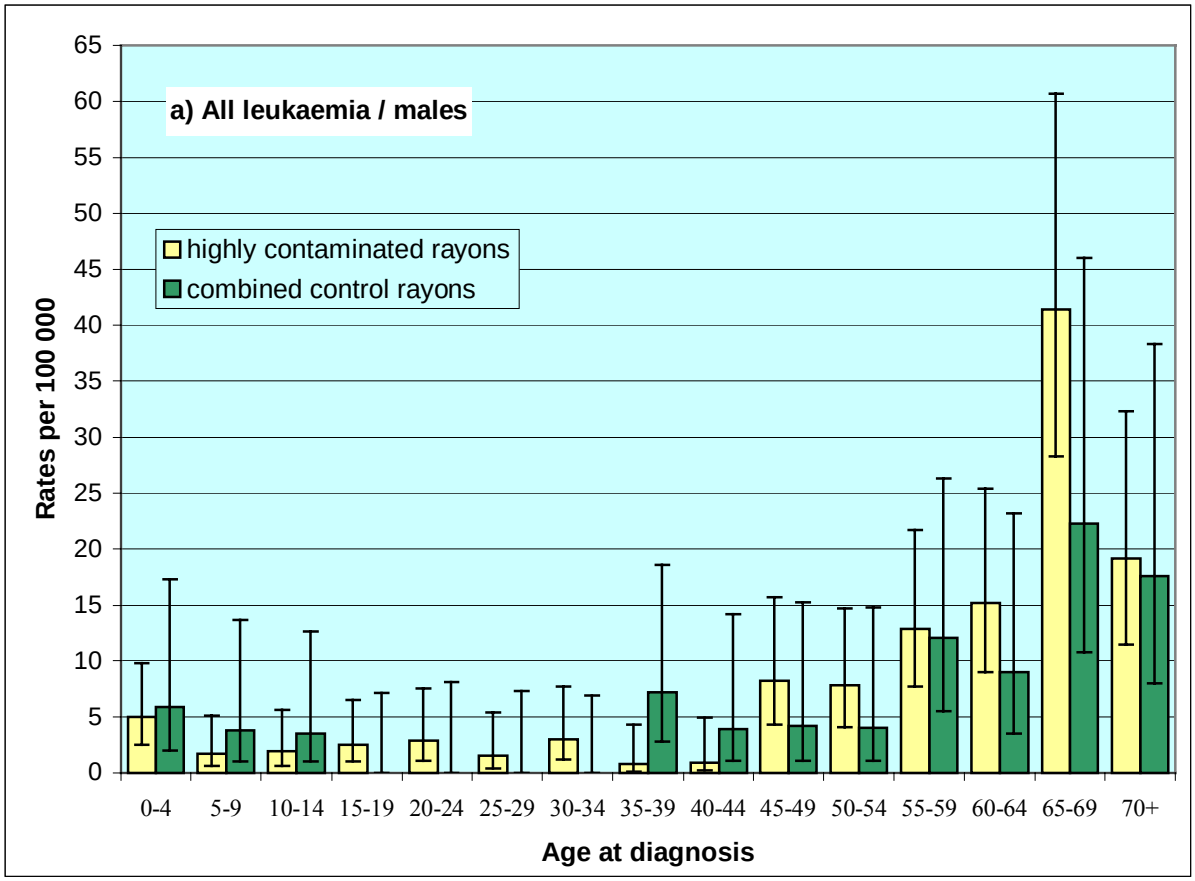
Fig 3.8 Standardized (world standard) leukaemia incidence rates (per 100 000) in children (boys and girls) over the three study periods. The figures indicate the number of cases that the rates are based on (cf table 3.2.)

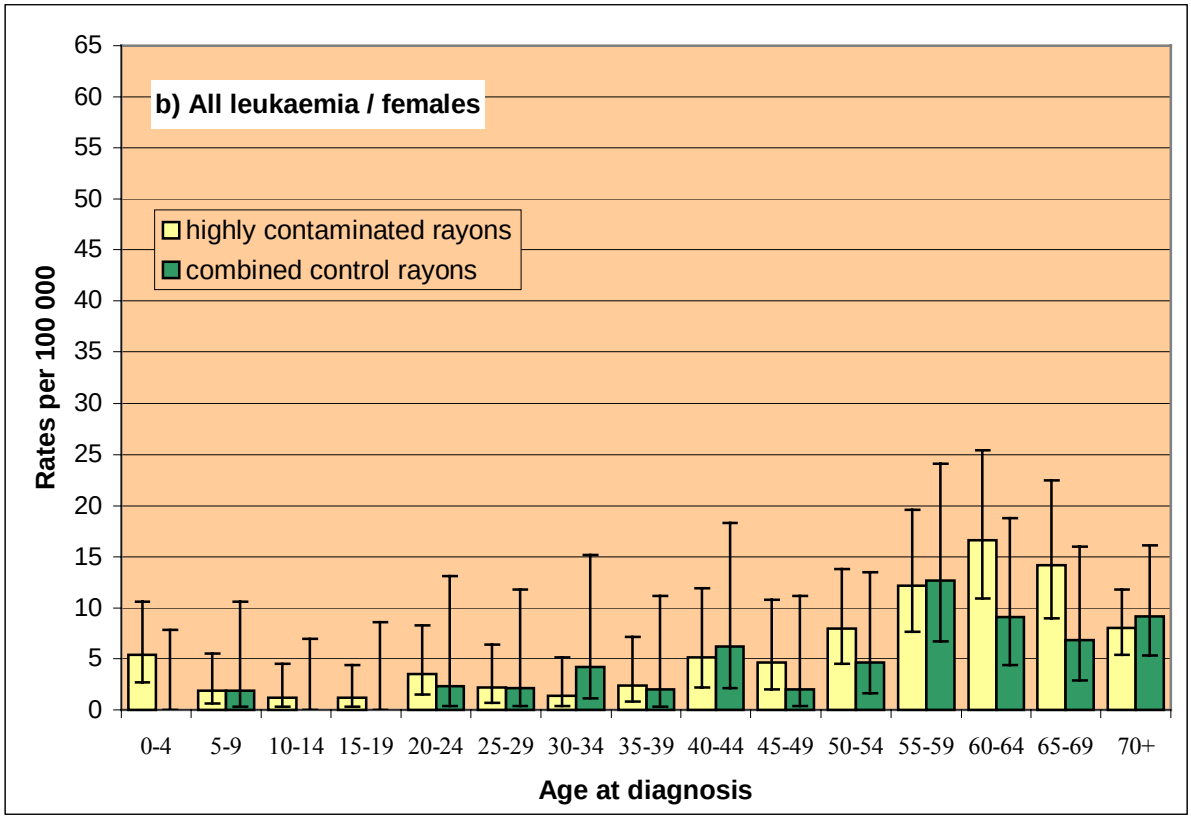
The results of the comparison of standardized incidence rates in the highly contaminated rayons of the Bryansk oblast and the combined control rayons of the Kaluga oblast show no statistically significant difference, neither for all leukaemia, nor for all leukaemia excluding CLL. There is a slightly increasing secular trend in the standardized incidence rates in adults of all leukaemia as well as of CLL. This increase is more marked in the combined control rayons than in the highly contaminated rayons. The standardized incidence rates in children have clearly increased over time in the combined control rayons, but have decreased in the highly contaminated rayons.

3.5. AGE-SPECIFIC INCIDENCE RATES

An important aspect in the description of leukaemia incidence is the specific incidence in the different age groups. Age-specific incidence rates of all leukaemia and all leukaemia excluding CLL in 5-year age groups are given in fig 3.9 for males (a, c) and females (b, d) in the highly contaminated and the combined control rayons. The age-specific incidence rates were calculated over the entire study period (1980–1998) in order to increase statistical power. Table 3.4 gives the age-specific incidence rates with the corresponding 95% CI's.

The age-specific incidence rates in children are higher for boys in the combined control rayons than in the contaminated rayons, but the opposite is true for the incidence in girls. This difference is not significant at the 95% level of confidence. In adults (apart from the age group 35-44), there is a tendency towards higher rates in the contaminated rayons in comparison with the combined control rayons for all leukaemia as well as for all leukaemia excluding CLL. This tendency is also not significant.


a) All leukaemia / males
highly contaminated rayons
combined control rayons
Rates per 100 000
0
5
10
15
20
25
30
35
40
45
50
55
60
65
0-4
5-9
10-14
15-19
20-24
25-29
30-34
35-39
40-44
45-49
50-54
55-59
60-64
65-69
70+
Age at diagnosis


b) All leukaemia / females
highly contaminated rayons
combined control rayons
Rates per 100 000
0
5
10
15
20
25
30
35
40
45
50
55
60
65
0-4
5-9
10-14
15-19
20-24
25-29
30-34
35-39
40-44
45-49
50-54
55-59
60-64
65-69
70+
Age at diagnosis

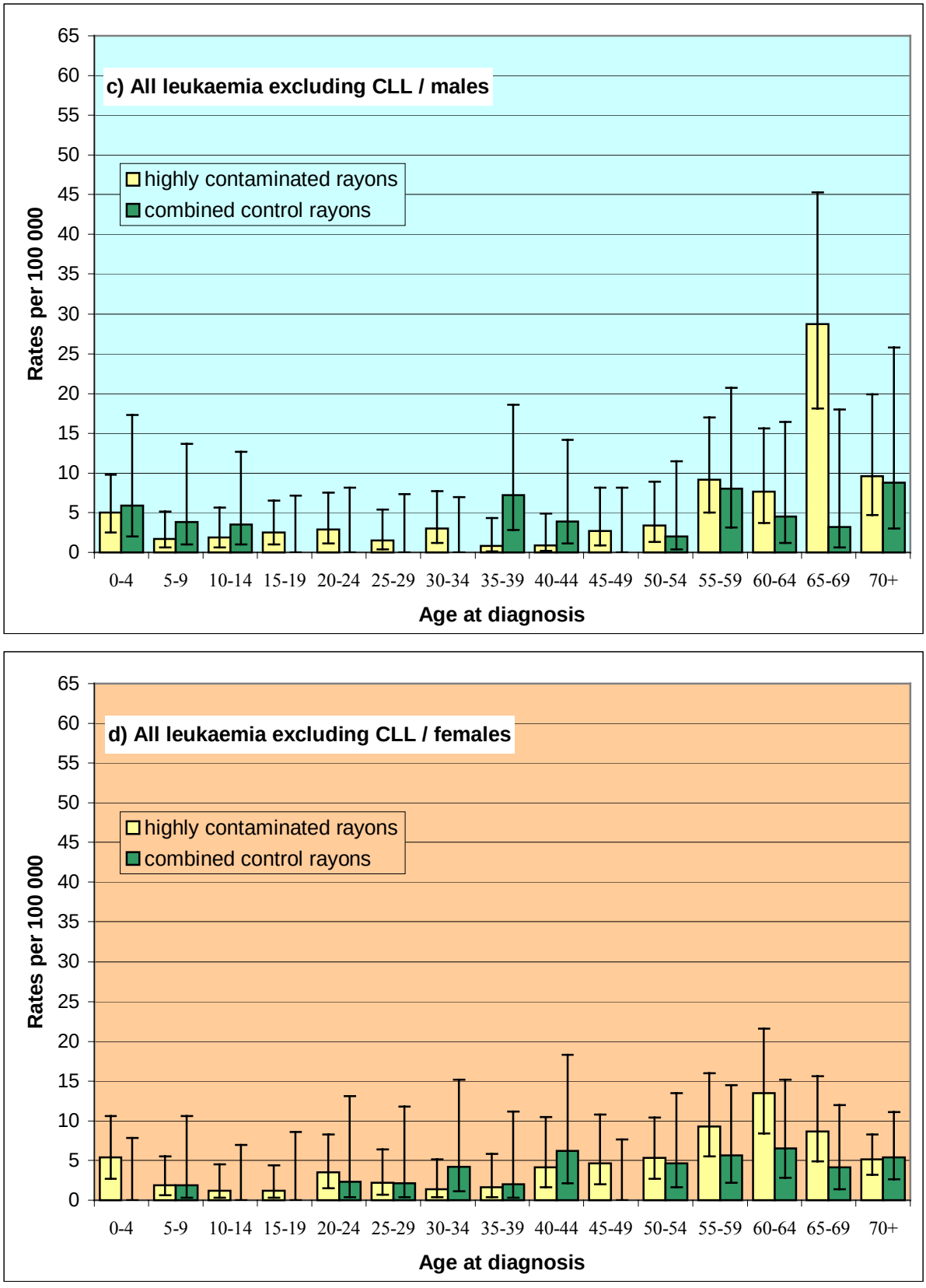


Fig 3.9 Age-specific incidence rates (per 100 000) over the entire study period (1980-1998). Vertical bars indicate 95% CI's according to Poisson

Table 3.4 Age-specific incidence rates (per 100 000) with 95% CI's according to Poisson over the entire study period (1980-1998)

			0-4	5-9	10-14	15-19	20-24	25-29	30-34	35-39	40-44	45-49	50-54	55-59	60-64	65-69	70+
All leukaemia	**male**	**HCR***	5 2.5;9.8	1.7 0.6;5.1	1.9 0.6;5.6	2.5 1;6.5	2.9 1.1;7.5	1.5 0.4;5.4	3 1.2;7.7	0.8 0.1;4.3	0.9 0.2;4.9	8.2 4.3;15.7	7.8 4.1;14.7	12.9 7.7;21.7	15.2 9;25.4	41.4 28.3;60.7	19.2 11.5;32.3
		CCR^	5.9 2;17.3	3.8 1;13.7	3.5 1;12.7	0 0;7.1	0 0;8.1	0 0;7.3	0 0;6.9	7.2 2.8;18.6	3.9 1.1;14.2	4.2 1.1;15.3	4 1.1;14.8	12.1 5.5;26.3	9 3.5;23.2	22.3 10.8;46	17.6 8;38.3
	female	**HCR**	5.4 2.7;10.6	1.9 0.6;5.5	1.2 0.3;4.5	1.2 0.3;4.4	3.5 1.5;8.3	2.2 0.7;6.4	1.4 0.4;5.1	2.4 0.8;7.1	5.1 2.2;11.9	4.6 2;10.8	7.9 4.5;13.8	12.2 7.6;19.6	16.6 10.9;25.4	14.2 9;22.5	8 5.4;11.8
		CCR	0 0;7.8	1.9 0.3;10.6	0 0;6.9	0 0;8.6	2.3 0.4;13.1	2.1 0.4;11.8	4.2 1.1;15.2	2 0.3;11.2	6.2 2.1;18.3	2 0.4;11.2	4.6 1.6;13.5	12.7 6.7;24.1	9.1 4.4;18.8	6.8 2.9;16	9.2 5.3;16.1
All leukaemia excluding CLL	**male**	**HCR**	5 2.5;9.8	1.7 0.6;5.1	1.9 0.6;5.6	2.5 1;6.5	2.9 1.1;7.5	1.5 0.4;5.4	3 1.2;7.7	0.8 0.1;4.3	0.9 0.2;4.9	2.7 0.9;8.1	3.4 1.3;8.9	9.2 5;17	7.6 3.7;15.6	28.7 18.1;45.3	9.6 4.7;19.9
		CCR	5.9 2;17.3	3.8 1;13.7	3.5 1;12.7	0 0;7.1	0 0;8.1	0 0;7.3	0 0;6.9	7.2 2.8;18.6	3.9 1.1;14.2	0 0;8.1	2 0.4;11.5	8 3.1;20.7	4.5 1.2;16.4	3.2 0.6;18	8.8 3;25.8
	female	**HCR**	5.4 2.7;10.6	1.9 0.6;5.5	1.2 0.3;4.5	1.2 0.3;4.4	3.5 1.5;8.3	2.2 0.7;6.4	1.4 0.4;5.1	1.6 0.4;5.8	4.1 1.6;10.5	4.6 2;10.8	5.3 2.7;10.4	9.3 5.5;16	13.5 8.4;21.6	8.7 4.9;15.6	5.1 3.2;8.3
		CCR	0 0;7.8	1.9 0.3;10.6	0 0;6.9	0 0;8.6	2.3 0.4;13.1	2.1 0.4;11.8	4.2 1.1;15.2	2 0.3;11.2	6.2 2.1;18.3	0 0;7.6	4.6 1.6;13.5	5.6 2.2;14.5	6.5 2.8;15.2	4.1 1.4;12	5.4 2.6;11.1

HCR* - highly contaminated rayons (mean population: 226 600)

CCR^ - combined control rayons (mean population: 88 466)

4. DISCUSSION

4.1. COMPLETENESS AND QUALITY OF THE DATA

The initial database at the local cancer registry consisted of 331 routinely registered leukaemia cases for the years 1980 to 1998 in the rayons under study. The active search for cases previously diagnosed but not registered added 36 cases to the project data base. The search was conducted at all medical and administrative institutions where information on patients with leukaemia might be found. It can therefore be assumed that all cases diagnosed between 1980 and 1998 in the rayons under study were finally included in the project data base.

In spite of this, the possibility that not all patients having leukaemia were diagnosed as such cannot be dismissed. This is especially true for the older age-groups in rural regions. However, there is no indication that the extent of underdetection varied during the study period. If anything, the level of detection might have been expected to improve with an improving health care system in the late 1980s and to subsequently deteriorate during the 1990s with the crisis of the health care system after the disintegration of the Soviet Union. This would also apply especially to the elderly, who often cannot afford the previously cost-free public health service. A general under-registration of cancer incidence rates in Russia for the age-groups 70+ has been reported [SHK 99], and is highly likely to have also occurred in the present study. Only the order of magnitude remains speculative. Such an under-detection of cases on a stable level, however, is not important in relation to the assessment of a possible radiation effect, neither in the regional nor in the temporal analyses.

Furthermore, varying levels of completeness of cancer registration in Russia in the 1980s and 1990s due to changing coding practises of death certificates have been observed [SHK 99]. This effect would only concern cases added to the data base by the evidence of the death certificate only (DCO cases). Due to the extensive follow-up on every case included, there are no DCO cases in the present study.

In order to optimize the quality of the data, all information included in the project data base was verified directly at the responsible medical and administrative institutions. This led to the exclusion of 34 cases: in 18 ‘non-cases’ the initial diagnosis proved to be wrong, whereas 16 ‘non-cases’ were due to technical errors (miscoding of a diagnosis other than leukaemia as leukaemia, wrong addresses, dates, etc.). The fact that only 18 cases (4.9%) had to be excluded from the project data base due to misdiagnosing testifies to the high level of accuracy and precision of the initial diagnoses. This is in line with the experience of an international haematologic panel reviewing leukaemia cases from the Ukraine, where the ‘haematologists and haemopathologists on the panel were in agreement with one another and with the previously reported diagnoses and classifications of about 90% of the cases of acute and chronic leukaemia in the study’ [DYA 02]. The accuracy in this study was supported by the fact that ICD 9 with its exhaustive and mutually exclusive categories had been initially used as opposed to being attributed to the cases in the course of the study.

The frequency distributions of the different types of leukaemia in the different study rayons and periods are homogeneous, as are the age and sex distributions. An external comparison furthermore shows these parameters to be in line with international experience [SEE 03, CIN 97]. These findings indicate high internal and external validity of the data.

It is remarkable but most probably purely coincidental that the order of magnitude of false-negative cases (36 cases added to the project data base through active detection, corresponding to 10.9% of the 331 cases in the initial database) and of false-positive cases (34 cases omitted, corresponding to 10.3% of the initial cases) is the same. This implies that the *a priori* error that would have occurred in an analysis previous to the extensive data-check is equal to the *a posteriori* error and must, in any case, be smaller than 10% of the number of cases.

4.2. CONTINUITY OF THE DOCUMENTATION AND POSSIBLE BIASES

The absence of abrupt, statistically significant changes in incidence rates over time or between the groups of study rayons points towards the continuity of the documentation of the cases. It has been suggested that fear in the population and increased awareness among medical doctors might result in an expectation or a detection bias. Both biases would lead to elevated incidence rates directly after the accident and a subsequent decrease. In the case of an expectation bias the incidence rates would simply return to the pre-accident level. In the case of a detection bias the rates would fall below the pre-accident rates after the initial increase before returning to the actual level. There is no indication of either an expectation or a detection bias in this study.

A further source of a possible bias is the migration of the population from the highly contaminated to the control regions, leading to a misclassification of exposed individuals. Demographic data on the age and sex structure of the population of the rayons under study were contributed by the Oblast Statistics Committee (Oblkomstat) on the basis of the censuses in 1979 and 1989. The change in population size clearly exceeds the effect of a change in birth rate. This is also evident when assessing the demographic structure of the different populations. The changes in the study regions must therefore be partly due to migration. Unfortunately, it is difficult to obtain detailed information on migration on the rayon level, especially where the people might have migrated from or to [KOR 03]. Nevertheless, several aspects suggest that a possible migration effect would not strongly bias the overall results of this study:

Migration may be compulsory or chosen, even if it is an official resettlement of inhabitants of some highly contaminated areas by the local (oblast) authorities. The compulsory resettlement concerns only extremely highly contaminated areas and mostly happened fairly shortly after the accident, before high individual doses had been accumulated. Since any type of official resettlement took place within the same oblast or even within the same rayon, the population increase in the control rayons in the Kaluga oblast cannot be due to people officially resettled from the extremely highly contaminated areas in the Bryansk oblast. Due to much lower contamination, there was no compulsory resettlement at all in the Kaluga oblast. People migrating from the slightly contaminated study rayons (which are all located in the Kaluga

oblast) to the control rayons in the Kaluga oblast might account for some of the population increase in the control rayons [KOR 03]. Their radiation risk, however, is so low (cf. 3.2.) that it is negligible in view of the remainder of the control cohort.

People may also migrate on their own accord for various reasons not directly linked to the radiation, i.e. for economic reasons or simply because they have family in other places, for example in Moscow [KOR 03]. These people would not necessarily be those with the highest risks. Since this type of migration would have occurred similarly in the highly contaminated and the slightly contaminated rayons, it would lead to non-differential misclassification.

For the above stated reasons, any migration might lead to a slight underestimation of the risk in the highly contaminated rayons in the worst case, but would not result in an overestimation of the risk in the control rayons.

4.3. STRENGTHS AND LIMITATIONS OF THE STUDY

The strengths of the present study are the completeness and the outstanding quality of the data: the 333 cases in the final project data base must be considered as the complete number of cases diagnosed in the study rayons between 1980 and 1998 and the diagnoses can be seen as incontestable. The results of the analyses thus give an accurate picture of the leukaemia incidence rates in the study rayons and periods, which allows a realistic assessment of a possible effect of the radiation released from the Chernobyl Nuclear Power Plant in 1986.

The study cohorts were formed according to the official mean annual effective dose they have been subjected to due to the Chernobyl accident in addition to their average annual dose (mainly natural and medical exposure) of about 2.4 mSv. In the years 1986 to 1995, this additional average annual dose amounted to 2.29 mSv in the highly contaminated rayons, to 0.74 mSv in the slightly contaminated rayons and to 0.035 mSv in the control rayons. Joining the population of the slightly contaminated rayons and of the control rayons to form the combined control cohort results in higher statistical power. This is possible without the loss of power in the risk group, for the cumulative attributable risks at 0.74 mSv are negligible in view of the size of the study cohort (cf 3.2).

The study does not allow the estimation of risk coefficients because no individual dosimetry can be provided. Mean doses are computed for the inhabitants of settlements, so that the dose range would be wide when estimating the dose for an actual individual from this information. The computation of risk coefficients would require individual dosimetry and a sufficient control of confounding factors (such as exposure to other risk factors) in a cohort or preferably even a case-control study.

4.4. ATTRIBUTABLE RISKS OF LEUKAEMIA IN THE STUDY COHORT AND THEIR DETECTION

The attributable lifetime risk of leukaemia in the population of the highly contaminated rayons is estimated to be 24 cases, based on the risk factors from the Life Span Study of the Japanese cohort. These cases are assumed to occur in addition to a calculated baseline estimate (without the radiation factor) of 703 cases, adding up to a total of 727 cases (including the assumed radiation factor). When calculating the 95% confidence interval (95%CI 651; 755) it becomes clear that such an influence, even if present, would not be statistically detectable. This is all the more true for the smaller numbers of radiation-related (9.4) and baseline (64) cases estimated for the years 1989-1994 in the same cohort (95%CI 48.74; 80.25) [SAC 92].

4.5. RESULTS OF THIS STUDY IN COMPARISON TO OTHER EXPOSED COHORTS

An increase of MDS after the Chernobyl accident, as postulated by some Eastern scientists [IVA 97], is highly unlikely although MDS is thought to be inducible by ionizing radiation [AUL 98, NIS 01]. However, there is no large-scale experience or estimation of risk co-efficients, for example from Japan, as MDS had not yet been defined as such. The risk co-efficients for acute leukaemia from the Japanese studies must thus be seen as an integral measure of the risks of MDS *and* acute leukaemia. In this study MDS is not included mainly because the quality of diagnosis could not be assured, especially for the early years. Nevertheless, it may be assumed that a dramatic increase in MDS would have been noticed, as 25%-40% of MDS turn into acute leukaemia in the course of the disease [YOS 96]. This would have reflected in the present analysis.

4.5.1. CHILDREN

Leukaemia is a rare disease in childhood: in this study, only 35 cases occurred between 1980 and 1998 in the children (0-14 years) of the study cohort (1.84 cases per year). Their distribution over the years and the study periods leads to very small numbers of cases on which the individual incidence rates are calculated. This implies that the power of the statistical analysis is very low. Nevertheless, the absence of an increase in the years after the Chernobyl accident or of elevated rates in the contaminated versus the control rayons indicates the absence of a considerable radiation effect in the studied children.

These findings are in line with the findings of studies of similar methodology and quality of larger childhood populations in the contaminated areas of Belarus, Russia, and the Ukraine [BEC 02, GAP 01b, IVA 96]. Even a study on the subgroup of infants, who seem to be especially radio-sensitive [STE 56], could not detect elevated incidence rates for Belarus [IVA 98]. It therefore seems highly unlikely that the increase in infant leukaemia reported for Greece [PET 96] is due to radiation, as the contamination in Greece was lower than in Belarus by a factor of more than 10. This is also true for the average doses in Germany, where even in the more highly contaminated southern parts the doses remained well below those in Belarus or the highly contaminated Russian study regions (cf. tab. 4.1).

No detectable increase due to the radiation after the Chernobyl accident has been reported by the European Childhood Leukaemia-Lymphoma Study (ECLIS), which compiles data from 36 cancer registries of 23 countries. The authors observe ‘a slight increase in the incidence of childhood leukaemia in Europe’ but also find that ‘the overall geographical pattern of change bears no relation to estimated exposure to radiation resulting from the accident’ [PAR 96]. This supports the notion that the lack of a dose-effect relationship cannot be dismissed in epidemiologic reasoning.

4.5.2 ADULTS

There is no increase in leukaemia incidence rates in the post-accident periods in comparison to the pre-accident period. Moreover, the incidence rates in the contaminated rayons do not differ from those in the control rayons. Both are true for all leukaemia as well as for all leukaemia excluding CLL and no difference has been observed between the sexes. The age-specific incidence rates show no remarkable features apart from surprisingly low rates for the older age-groups (cf. 4.1).

These findings are in line with data from other cancer registries covering the most highly contaminated regions of the Commonwealth of Independent States [GAP 01a, PRI 95], even if the completeness and quality of the data might vary.

Some regions of the world such as Kerala, India, and Yangjiang, China, are known for their high natural background radiation. These two regions are populated by about 100 000 persons each. The total size of these two populations is comparable to that of the highly contaminated study rayons (222 000) but the mean doses after Chernobyl were much lower (between 1986 and 1995 about 2.29 mSv plus 2.4 mSv from natural background and medical exposure, altogether about 4.7 mSv per year). Cancer incidence rates and mortality in the populations continuously exposed to high background radiation (10-100 mSv per year [TUB 00]) have been monitored for years. There is no indication of an elevated cancer incidence rate or mortality in either of the regions [TAO 00, NAI 99]. Some authors postulate an adaptive response induced by chronic exposure to natural background radiation [GHI 02]. Nevertheless, a detection of elevated cancer incidence rates even in the populations more highly exposed due to the Chernobyl accident would be surprising in view of the cancer rates in the populations exposed to high natural background radiation.

No increase of cancer risks has so far actually been observed at doses below 200 mSv in epidemiological studies on the level of the general population. Cases that may be assumed to occur when extrapolating on the grounds of risk factors derived from higher doses and dose rates are therefore referred to as virtual cases [TUB 00] or hypothetical risks [BFS 03].

One possible explanation for this phenomenon is the fact that the calculation of the risk coefficients from the Life Span Study is based on comparatively high doses at a high dose rate. Yet not only the doses, but also the dose rates, are much lower in the studies in question than in Japan. For low Linear Energy Transfer (LET) radiations ‘it is evident that theoretical considerations, experimental results in animals and other biological organisms, and even some limited human experience suggest that cancer induction at low doses and low dose rates

should be less than that observed after high doses and dose rates'. For this reason the International Commission on Radiological Protection (ICRP) has introduced a *Dose and Dose Rate Effectiveness Factor* (DDREF) [ICRP 90].

Another possible explanation is the choice of the model used for the calculation of risks at low doses. The shape of the dose-effect curve at doses below 200 mSv is disputable and may be anything from a linear function without a threshold or a linear-quadratic to a quadratic function. The conservative linear no-threshold approach is used in radiation-protection, where it is vital not to underestimate the risks. The resulting risk coefficients at low doses, however, may actually be higher than the real risks [TUB 00].

4.6. PUTTING THE RISK IN PERSPECTIVE – A COMPARISON WITH OTHER RISK FACTORS

At this stage it seems important to compare the mean annual effective dose to the population in the contaminated areas of Russia after the Chernobyl accident with the doses due to other sources of ionizing radiation (table 4.1)

Tab 4.1 Doses due to various sources of ionizing radiation [BFS 03, MHH 01, MIC 01]

Source	Mean annual effective dose per person [mSv]
Chernobyl NPP accident in the highly contaminated rayons [for the years 1986-1995 altogether 22.9 mSv]	2.29
In the slightly contaminated rayons [for the years 1986-1995 altogether 7.4 mSv]	0.74
Natural background radiation in Germany (as is typical for Europe in general)	2.4
Chernobyl (mean dose in Germany today) [in 1986: mean dose 0.5 mSv, near the Alps 0.65 mSv, south of the Danube river 0.35 mSv, north of the Danube river 0.17 mSv]	0.01
Nuclear Power Plants in Germany	<0.01
X-ray computed tomography	3-20
X-ray of the chest	0.2
Mammography [if screened every two years between the ages of 50 and 69 altogether 5 mSv]	0.5
Flight Paris-Tokyo at 12 000 m	0.2
Annual limit for exposed professionals	20

It must be stressed that ionizing radiation may, even at very low doses at which to date no such effect has been observed, induce a certain stochastic risk of cancer. As in any risk assessment, the benefits of an exposure, for example a necessary diagnostic x-ray, must be weighed against its detrimental effects. And it goes without saying that any unnecessary exposure should be avoided.

The hypothetical risk at low doses should therefore be assessed in relation to the order of magnitude of the radiation doses received from other sources like the natural background radiation, especially when the exposure in question is the source of massive public concern as is the case after the Chernobyl accident. Ionizing radiation is a very good example of discrepancy between the actual risk and the emotions raised: whether a certain risk is acceptable in the public opinion often depends not so much on the dimension of the risk as on its perception in a society. Beyond the factual aspect, risk seems to be a socially constructed concept. Gender, education and social status are strongly correlated with risk judgement and attitude. There even is a theory that 'individuals select what and how much to fear as the product of a particular cultural bias and in order to support a given world view' [TUB 99].

Whether risks are avoidable clearly has little influence on the risk perception. This becomes evident when comparing the above-mentioned hypothetical cancer risks at low doses of radiation with other, real cancer risks. The International Agency for Research on Cancer estimates that 50% of all cancers could be avoided by changes in lifestyle (less exposure to tobacco, alcohol, the sun, changes in nutrition, and more physical exercise) [cited in TUB 99].

A special problem in the Commonwealth of Independent States is the actual decline in health and the increase in mortality in the population, which mainly affects middle-aged men. After a marked increase in the mid 1980s due to Gorbachev's anti-alcohol campaign, the male life-expectancy at birth has dropped by nearly 10 years to presently 56.1 years (Disability Adjusted Life Expectancy - DALE), while it is still 66.4 years for women [DEM 03]. Incidentally, the infant mortality remained stable during the same period, which indicates that the health care system in the field of obstetrics and neonatology is – so far – intact. The decrease in life expectancy is mainly due to deaths from 'accidents and intoxication' and from 'cardiovascular diseases', whereas the cancer mortality has decreased for both sexes [SKH 99]. Obviously, the unfavourable economic and insecure social situation as well as self-induced health risks play a major role in the decrease of life-expectancy, but are rarely consciously associated with it. Yet people tend to attribute any physical symptom to the radiation factor – regardless of whether they live in a highly contaminated rayon or not.

4.7. RELEVANCE AND IMPLICATIONS FOR PUBLIC HEALTH

The present study was designed to detect a possible increase of leukaemia incidence on the level of the general population in the rayons of Russia highly contaminated as a result of the Chernobyl Nuclear Power Plant accident. Although the findings of the study are not surprising considering the scientific knowledge, they are nevertheless acutely important in view of the beliefs of the general public.

The fear and apprehension caused by the overestimation of the radiation risks create a continuous stress situation and add to the present detrimental health conditions in the population. Moreover, people who attribute the cause of ill health to an external locus of control are less liable to show positive health behaviour than people with an internal locus of control. This would, obviously, also affect the degree of counter-measures personally taken by individuals in the contaminated regions, such as following the special guidelines for the preparation of food (vegetables, meat, etc.) to reduce the content of radio-nuclides.

It is therefore of utmost importance to communicate not only the results but also the reliability of the study and the soundness of the data to the affected people. But even if the general public might not overcome their mistrust especially of official information, the findings should at least influence official institutions: ideally, the study should persuade public health authorities to address the current health problems instead of attributing them to the radiation factor and remaining inactive.

5. ABSTRACT

BACKGROUND

Leukaemia, especially the acute types predominant in children, may be caused by ionizing radiation. After the Chernobyl Nuclear Power Plant accident on 26 April 1986, parts of Belarus, Russia and the Ukraine were contaminated with radionuclides. To date, over 270 000 people live in such contaminated regions in Russia. This study investigates whether the leukaemia incidence rates in these regions might have increased due to the radiation.

MATERIALS & METHODS

A prospective population-based cohort study with a control group was carried out. Cases of leukaemia previously not registered were actively sought for in medical and administrative institutions. Each case that had occurred in the study regions between 1980 and 1998 has been ascertained and verified. A descriptive analysis was then performed on the resulting data base which included 333 leukaemia cases.

RESULTS

There is a slight secular trend in the standardized incidence rates both in the highly contaminated and in the control regions. This increase, however, is more marked in the control regions. The incidence rates in children (0-14) in the highly contaminated regions decrease between the pre-accident (1980 to 1986) and the first post-accident period (1987-1992) and show a slight increase towards the second post-accident period (1993-1998), whereas the incidence rates in the control regions show exactly the opposite dynamic. This makes a connection between the dynamics of the incidence rates and the radiological situation highly improbable.

The comparative analysis of the leukaemia incidence rates has not revealed a statistically significant difference between the population of the highly contaminated regions of the Bryansk oblast and the combined control regions of the Kaluga oblast.

CONCLUSIONS

There is so far no indication of an increase in leukaemia incidence rates in the general population, neither for children nor for adults. This does not contradict the current radiobiological knowledge that cancer, especially leukaemia, can be caused by ionizing radiation. The number of expected radiation-induced cases based on the risk estimates from the Japanese cohort lies within the 95% confidence limits of the spontaneous incidence rates. It would therefore, if at all present, not be statistically detectable in a population of 222 000 with a spontaneous rate of 5.4/100 000 in men and 3.3/100 000 in women in the control regions. Considering the latency periods and the age-dependent risk-curve of radiation-induced cancers, it is highly unlikely that a radiation-related increase in leukaemia or solid tumour incidence rates will become obvious in the future.

The fear and apprehension caused by the overestimation of the radiation risks create a continuous stress situation and add to the present detrimental health conditions in the population. It is therefore of utmost importance to communicate not only the results but also the reliability of the study and the soundness of the data to the affected people.

5. ZUSAMMENFASSUNG

HINTERGRUND

Leukämien, insbesondere die akuten Formen, die im Kindesalter vorherrschen, können durch radioaktive Strahlung induziert werden. Durch den Unfall in Tschernobyl am 26. April 1986 sind Teile von Belarus, Russland und der Ukraine radioaktiv kontaminiert worden. Bis heute leben in Russland über 270.000 Menschen in solchen kontaminierten Gebieten. Die vorliegende Studie untersucht, ob die Leukämieinzidenzen in diesen Gebieten aufgrund der radioaktiven Strahlung angestiegen sind.

MATERIAL & METHODEN

Zu diesem Zweck wurde eine bevölkerungsbezogene, prospektive Kohortenstudie mit einer Kontrollgruppe durchgeführt. Jeder Leukämiefall der Jahre 1980-1998 aus den Studienregionen wurde genau nacherhoben und verifiziert. Zudem wurde aktiv in Krankenhäusern und Behörden nach nicht erhobenen Fällen gesucht. Die 333 Leukämiefälle, die sich letztendlich in der Datenbank befanden, wurden deskriptiv analysiert.

ERGEBNISSE

Die standardisierten Inzidenzen zeigen über die Jahre einen leicht ansteigenden Trend, sowohl in den kontaminierten als auch in den Kontrollregionen. Dieser Anstieg ist ausgeprägter in den Kontrollregionen. Die Inzidenzen bei Kindern (0-14 Jahre) fallen in den kontaminierten Regionen zwischen der Periode 1980-86 und der Periode 1987-1992 ab und steigen dann in der Periode 1993-98 wieder leicht an, wohingegen die Inzidenzen in den Kontrollregionen genau die umgekehrte Dynamik zeigen. Dies macht einen Zusammenhang mit der radioaktiven Strahlung höchst unwahrscheinlich.

Die vergleichende Analyse zeigt keinen statistisch signifikanten Unterschied in den Inzidenzen zwischen den kontaminierten Regionen und den Kontrollregionen.

SCHLUSSFOLGERUNGEN

Es gibt keinen Hinweis auf einen Anstieg der Leukämieraten in der Allgemeinbevölkerung, weder bei Kindern noch bei Erwachsenen. Dies widerspricht nicht der strahlenbiologischen Erkenntnis, dass Tumoren, insbesondere Leukämien, durch radioaktive Strahlung induziert werden können. Die mittels der Risikokoeffizienten aus den japanischen Studien errechnete Anzahl der strahleninduzierten Leukämiefälle liegt innerhalb der 95% Konfidenzintervalle der jährlichen Fluktuation der Spontanraten. Solch induzierte Fälle wären daher – falls vorhanden – bei einer exponierten Bevölkerung von ca. 222.000 und einer in den Kontrollregionen beobachteten Spontanrate von 5,4/100.000 (Männer) bzw. 3,3/100.000 (Frauen) statistisch nicht nachweisbar. Bedenkt man die Latenzzeiten und die altersabhängige Risikostruktur strahleninduzierter Tumore, ist ein Anstieg sowohl der Leukämieraten als auch der Raten solider Tumore aufgrund des Reaktorunfalls in Tschernobyl in der Zukunft extrem unwahrscheinlich.

Die Ängste und Befürchtungen, die durch die Überschätzung der Risiken durch die radioaktive Strahlung entstanden sind, haben zu einer persistierenden Stresssituation für die Betroffenen geführt. Dieser Stress wirkt sich zusätzlich zu den aktuellen ökonomischen und sozialen Faktoren negativ auf die Gesundheit der Bevölkerung aus. Es ist daher wichtig, den Betroffenen nicht nur die Ergebnisse der vorliegenden Studie, sondern insbesondere auch die Qualität der zugrunde liegenden Daten glaubwürdig zu vermitteln.

6. ABBREVIATIONS

ALL	**(204.0)** acute lymphoid leukaemia
ALNOS	**(208.0)** acute leukaemia, not otherwise specified
AML	**(205.0)** acute myeloid leukaemia
AUL	**(208.0)** acute undifferentiated leukaemia
BOC	Bryansk Oblast Clinic БОБ – Брянская областная больница
BOOD	Bryansk Oblast Oncological Dispensary БООД – Брянский областной онкологический диспансер
BOPC	Bryansk Oblast Paediatric Clinic БОДБ – Брянская областная детская больница
Bq	Becquerel
BY	Belarus
CC	City Clinic ГБ – городская больница
CD	*Cluster of Differentiation*
CDL	Clinical-Diagnostic Laboratory КДЛ – клинико-диагностическая лаборатория
95%-CI	95%- confidence interval
Ci	Curie
CIS	Commonwealth of Independent States (founded in December 1992. Members are: Azerbaijan, Armenia, Belarus, Georgia, Kazakhstan, Kyrgystan, Moldova, Russia, Tajikistan, Turkmenistan, Uzbekistan and the Ukraine)
CLL	**(204.1)** chronic lymphoid leukaemia
CML	**(205.1)** chronic myeloid leukaemia
CMMoL	chronic myelomonocytic leukaemia
CLNOS	**(208.1)** chronic leukaemia, not otherwise specified
CR	Cancer Registry
CRC	Central Rayon Clinic ЦРБ – центральная районная больница
DCO	*Death Certificate Only*
df	*degree(s) of freedom*
EST	Esterase
ERR	*Excess Relative Risk*
Gosagroprom	State Committee of Agricultural Industry
Goskomepidnadzor	State Committe of Epidemiological Surveillance
Goskomgidromet	State Committee of Hydrometeorology of the USSR
Gy	Gray
IARC	*International Agency for Research on Cancer*
ICD-9	*International Classification of Diseases, Injuries and Causes of Death, 9th Revision*

KOC	Kaluga Oblast Clinic КОБ – Калужская областная больница
KOOD	Kaluga Oblast Oncological Dispensary КООД – Калужский областной онкологический диспансер
KOPC	Kaluga Oblast Paediatric Clinic КОДБ – Калужская областная детская больница
LDH	Laktate Dehydrogenase
LNOS	**(208.9)** leukaemia, not otherwise specified
LET	Linear Energy Transfer (of different types of radiation)
MDS	Myelodysplastic syndromes МДС – Миелодиспластический синдром
MRRC RAMS	Medical Radiological Research Centre of the Russian Academy of Medical Sciences МРНЦ РАМН – медицинский радиологический научный центр Российской академии меднаук
OAL	**(206.0, 207.0)** other acute leukaemia
OC	Oblast Clinic ОБ - областная больница
OCL	**(205.8, 207.1)** other chronic leukaemia
OOD	Oblast Oncological Dispensary ООД- областной онкологический диспансер
OPC	Oblast Paediatric Clinic ОДБ – областная детская больница
PAL	Patho-Anatomical Laboratory ПАЛ -патолого-анатомическая лаборатория
PAS	Periodic Acid-Schiff Reaction
POC	Paediatric Oblast Clinic ДОБ детская областная больница
POX	Peroxidase
RAEB	**(284.9)** refractary anaemia with excess blasts РАИБ - рефрактерная анемия с избытком бластов
Rosgydromet	Federal Service for Hydro-meteorology and Environmental Monitoring
RR	Relative Risk
RU	Russia
Sv	Sievert
UA	Ukraine
ZAGS	Vital Registration Department ЗАГС – Запись актов гражданского состояния

7. GLOSSARY

Absorbed dose: Energy which is transferred by radiation to matter per unit mass. This dose is given in Gray (Gy), where 1 Gy = 1J/kg.

Becquerel: measure for the activity of radionuclides, i.e. for the number of decays per time interval, where 1 Bq = 1 decay/sec.

Blast cells: undifferentiated blood cells which are normally found in the bone marrow and only in very small quantities in the peripheral blood.

Cancer Registry: the term *Cancer Registry* is used – if not otherwise stated – for population based cancer registries.

95%-Confidence interval (95%-CI): Range around a mean in which 95% of the values of a sample survey are located. For a Poisson distribution this is approximately:

95%-CI = [n – 1.96*√n; n + 1.96*√n].

Dispensary (*диспансер*): specialized (in view of the disease) therapeutic and prophylactic institution which screens for, treats and registers patients with a specific disease. Additionally, definite population groups are monitored to prevent a disease or the spreading of a disease. [MDF 92]

Dispenserisation (*диспансеризация*): screening and therapeutic monitoring of an entire population. The responsibility of the dispensary follows the place of residence, i.e. the population is monitored entirely without overlap. The monitored population is regularly invited for screening. Patients are treated with the most modern methods (available *author's comment*). Prophylactic measures and amelioration of the environment is part of the dispensarisation. [MDF 92]

Equivalent dose: different types of radiation vary in their relative biological effectiveness (RBE). To obtain the equivalent dose, the absorbed dose (↑) is multiplied with an official radiation-specific weighting factor (w_R) that is set by the *International Commission on Radiological Protection* (ICRP); for example, w_R for photons (γ- or x-rays) is 1, for neutrons it is 20. The equivalent dose is given in Sievert (Sv), where 1Sv = 1 J/kg.

***Excess Relative Risk* (ERR):** relative risk (↑) exceeding 1. ERR=RR-1= $CI_{EX}/CI_{Non\text{-}EX}$-1.

***Expectation bias*:** increased perception (and registration) of (presumed) effects because of the expectation of the observer.

Gray: unit of the absorbed dose (↑), where 1 Gy = 1J/kg

Incidence: (rate) describes the occurrence of a disease in relation to a population over a specified time interval. It is usually given per 100 000 persons.

I = cases in the time interval x / mean population in the time interval x.

Khozraschet (*хозрасчет*): economic tendering of account. Important constituant of the perestroika (↑) under Gorbachev, in which state-owned enterprises were expected to produce economically.

***Low dose*:** often not specified. The *United Nations Scientific Committee on the Effects of Atomic Radiation* (UNSCEAR) defines *low dose* as dose below 200 mSv [UNS 00].

Median: middle-valued observation when all the observations are ranked in order of value [MOU 98].

Oblast (*область*): administrative subunit of a republic of the former Soviet Union. They are formed on the grounds of the number of inhabitants, not on geographic or historic features. The population of an oblast is 1.5 – 2 million and, correspondingly, they vary a lot in geographic size. Oblasts are further subdivided into rayons (↑).

Oncological dispensary: (↑Dispensary) institution specialized in screening, therapy, follow-up and registration of a specific disease.

Perestroika (*перестройка*): rebuilding. Term introduced politically by Gorbachev for the restructuring of governmental and societal structures of the Soviet Union.

Poisson-distribution: describes the probability of events in space or time which occur at a defined frequency.

***Power*:** 1 - β, i.e. 1 – the probability of erroneously accepting the null-hypothesis.

Proliferation, clonal: growth by division of a single cell. Formation of a clone, i.e. a group of genetically identical cells.

Radioactivity: decay of atomic nuclei, the so-called radionuclides. Radionuclides transform into other nuclides e.g. by emitting specific radiation such as α-, β-, or γ-radiation. There are natural as well as man-made radionuclides. The **activity** of nuclides is measured as the number of decays per time interval. Its unit is **Becquerel**, where 1 Bq = 1 decay/sec.

Rate: (↑) Incidence.

***Rate Ratio*:** ratio of two rates (incidences) (↑)

Rayon (*район*): administrative subdivision of an oblast (↑) or a larger town. A rayon has 70 000 – 150 000 inhabitants.

Relative Risk (RR): measure to describe the effect of a harming agent. The RR is the ratio of the probability to incur a disease for the exposed (CI_{EX}) versus the non-exposed ($CI_{Non\text{-}EX}$). $RR= CI_{EX}/CI_{Non\text{-}EX.}$

***Screening*:** examination of groups of population (population at risk) in order to detect certain diseases at an early stage.

Sievert: unit for the equivalent dose (↑), where 1Sv = 1 J/kg.

Uchastok (*участок*): smallest unit for the delivery of public health care, administrative subdivision of a rayon (↑). The uchastok comprises 3 000 – 4 000 persons, to whom primary health care is delivered by a general practitioner, a gynaecologist and obstetrician, a paediatrician, and several nurses.

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NOTE

When transferring the cyrillic alphabet into latin, an English phonetic transcript was used rather than a scientific transcript. Probably because of its distribution in the World Wide Web, the phonetic transcript has been widely accepted in the past years in preference to other systems.

Words and geographic names as well as names that are customarily spelt deviantly from the phonetic system are spelt in the customary way.

ANNEXE 1

SOME IMPORTANT FRAGMENTS FROM THE METHODOLOGICAL RECOMMENDATIONS:

"1.5. The mean cumulative effective dose received by all residents of the settlement has been conservatively admitted to be the mean cumulative dose in adults. According to the dosimetric surveillance of the population in the regions contaminated after the Chernobyl accident in the period from 1986 to 1995, the mean annual effective dose to children of various ages did not exceed the mean dose to adults of the same settlement.

1.7. The external radiation dose is the dose due to γ-radiation of all deposited radionuclides with a half-life ranging from several hours to 30 years. The contribution of each of the radionuclides to the dose accumulated for 9.7 years (from 1986 to 1995) exceeds 0.1%. According to modelled estimations, the effective dose due to β- and γ-radiation directly from the radioactive cloud that moved over the settlements of the Russian Federation was less than 5% of the mean cumulative dose for the first year following the accident and is not taken into consideration in the current methodological recommendations. Modelled estimations showed that the contribution of external distant and contact exposure of the skin to β-emitted radionuclides is negligible and has therefore not been accounted for in the recommendations.

1.8. The internal radiation dose is due to ^{137}Cs, ^{134}Cs, ^{90}Sr, ^{89}Sr which enter the body via foodstuffs. A contribution of the inhaled radionuclides to the internal radiation dose from both the radioactive cloud and resuspension of the deposited radionuclides has not been accounted for except for ^{137}Cs and ^{134}Cs. …The results of autopsy tissue of residents of the Bryansk oblast showed that the contribution of isotopes of plutonium to the effective dose did not exceed 1%. The contribution of other radionuclides - except for those mentioned above - that were deposited on the surface of vegetables shortly after the Chernobyl accident and accumulated for 9.7 years was also negligible." [MER 96]

ANNEXE 2

DETAILED DESCRIPTION OF THE VERIFICATION PROCESS

The correct diagnosis and up-to-date classification of leukaemia and lymphomas remains one of the most difficult diagnostic procedures in contemporary medicine.

The basis for the classification of the various cytological forms of leukaemia is the microscopic examination of blood and bone marrow smears, spinal fluid and exudation in serous spaces. Depending on the type of leukaemia and the individual course of the disease, further histological study of biopsies of lymphatic nodes or bone marrow may be necessary [GLU 98]. A more detailed classification of the type of the transformed cells is achieved by cytochemical methods [GLU 78, HAY 88]. Most of the haemato-oncological departments and laboratories of the city and oblast clinics, including the oncological dispensaries, are now able to carry out such procedures at reasonable quality [FAJ 80]. A contemporary diagnosis though requires supplementary immunophenotyping of the leukaemic cells as well as cytogenetic and molecular genetic analysis – technologies which were introduced only lately in the countries of the CIS [BAR 97, GLU 00a, BAI 01, LUG 01]

These new technologies have revolutionized the classification of leukaemia [BEN 95, BAI 99, WIL 99] and led to changes, leaving some classes of the ICD 9 incompatible with the ICD 10. A review of the cases diagnosed earlier thus led to new classification of some of the cases as formerly unknown subtypes of leukaemia.

However, as this study is conducted retrospectively on cases which have been diagnosed and classified mainly based on the morphological and cytochemical analysis of blood and bone marrow cells, the ICD 9 classification is preserved.

One of the difficulties in the verification of correct diagnoses is acute leukaemia of unspecified cell type (ICD 9: 208.0): This code may actually be attributed in two different cases, namely to 1) *acute leukaemia, not otherwise specified* (ALNOS) and 2) *acute leukaemia of unspecified cell type*. In the haematological departments of Russia (and formerly of the Soviet Union), such cases were identified as *acute undifferentiated leukaemia* (AUL) [FAJ 80, GLU 00]. As a rule, non-verified *acute leukaemia, not otherwise specified* (ALNOS) were found only in cancer registration documents. In some cases, the initial medical document could not be traced, in all other cases the diagnosis had been established posthumously, when cytochemical or other typing of the blast cells was impossible. If, on the other hand, the diagnosis 208.0 had been verified, the case was cytochemically and – sometimes - immunologically typed as *acute undifferentiated leukaemia* [BEN 95]. Some authors believe such leukaemia to be lymphoid [LUD 94] or myeloid [BEN 91, BEN 97, FRE 98], others postulate the existence of a biphenotypic form [HAN 93, LEN 99]. Even if these undifferentiated forms are extremely rare (1-2,5% of all cases of acute leukaemia), the cases in the study were taken as verified, as there were convincing indications in the medical histories.

From the point of view of classification, another veritable difficulty with using the ICD 9 is the absence of a code for myelodysplastic syndromes (MDS). All present classifications contain information about this clonal disease of the bone marrow, which develops on the grounds of a disorder of the stem cell [BEN 85, AUL 94, ROS 96, BEN 97, GUS 99, GLU 01]. MDS often transform into acute leukaemia [TRI 92], a number of MDS are thus assessed as preleukaemic conditions. Ukrainian authors have found that acute myeloid leukaemia in persons who had been irradiated due to the ChNPP accident is often preceded by MDS [SIV 01]. In the Russian haematological departments, some forms of MDS with a small share of blast cells were described as *small-percentage leukaemia*, which corresponds to *leukaemia with low count of blasts*.

The FAB classification, which accounts for the various forms of MDS, was used in the more important haematological centres in Russia since the middle of the 1980s. According to the FAB classification, the diagnosis *leukaemia with low count of blasts* which usually types as myeloid or myelomonoblast, corresponds to refractary anaemia with excess blasts (RAEB). RAEB is found in children as well as in adults [HAS 94, IVA 94, PAS 95].

Decisive for the diagnosis RAEB is the presence of 5-20% of blast cells in the bone marrow and up to 5% of blast cells in the peripheral blood in contrary to the diagnosis *acute myeloid leukaemia* which demands 30% blast cells in the bone marrow. RAEB is no longer a category of the myelodysplastic syndromes in the ICD 10 and all conditions in which myeloid blast cells in the bone marrow exceed 20% are classified as acute myeloid leukaemia.

According to WHO recommendations, even myelodysplasia with low count of blasts in the bone marrow – which were formerly diagnosed as *myelodysplastic syndromes* (in Russia: *refractary anaemia with excess blasts* OR *acute leukaemia with low count of blasts*) – should now be diagnosed as *acute myeloid leukaemia* [GLU 01]. In this study, two such cases were found in the medical histories, where the diagnosis *acute leukaemia with low count of blasts* was attributed along with the diagnosis MDS, RAEB. Those cases were coded as 205.0, i.e. *acute myeloid leukaemia*.

The myelodysplastic syndromes are known to be inducible by radiation just as acute leukaemia and chronic myeloid leukaemia [GLU 96, BEB 99], they are thus analysed together in this study.

The data collection, ascertainment and verification was carried in the oblast and rayon clinics where the initial medical documents are stored. The results of all the information found during the verification process was entered into a specially designed *Verification Card for Leukaemia Cases* (fig. A2.1).

The process of collection, ascertainment and verification is a multilevel process:

1ST LEVEL

Institution: Oblast Oncological Dispensary (OOD)
Source*:* Control Card of the cancer patient

The analysis of the Control Cards allows the comparison with the information that is stored in the database of the cancer registry. If inconsistencies are found, further research in other medical documents and institutions is initiated. The information on the Control Card consists of:

1.1. Surname, name, patronymic
1.2. Year of birth
1.3. Place of residence
1.4. Full written diagnosis, including clinical (acute, chronic) and cytological (myeloid, lymphoid, other) characteristics
1.5. ICD-9 code
1.6. Date of registration of the patient at the OOD
1.7. Date of exclusion of the patient from the files of the OOD
1.8. Information about in-patient treatment or other medical consultations
1.9. Diagnosis was made on the grounds of:
    1.9.1. blood analysis
    1.9.2. bone marrow punction
    1.9.3. clinical picture
    1.9.4. histological findings
1.10. instructions for autopsy
1.11. date of death

Cases were actively sought for in the registries of other blood disorders at the OOD:

- anaemia
  (of uncertain aetiology, hypoplastic, refractory, vit-B12-deficiency, autoimmune, etc.)
- lymphoma
- leukaemoid reaction
- thrombocytopaenia of uncertain aetiology
- cytopaenia.

Name, surname	Card number	Sex	Date of birth	Address	Rayon code	Date of death

Code of disease	Verifi. code	Date of diagnosis	Verifi. date	Age	Method of verification	Diagnosis (text)

SOURCES OF THE DATA

1. Medical History yes☐ no☐
2. Out-patient Card yes☐ no☐
3. Control Card of dispensary follow-up yes☐ no☐
4. Notification of a cancer case diagnosed for the first time yes☐ no☐
5. Records in the journal of Clinical-Diagnostic Laboratory yes☐ no☐
6. Blood smears yes☐ no☐
7. Blood analyses (text) yes☐ no☐
8. Bone marrow smears yes☐ no☐
9. Other medical documents yes☐ no☐
10. Journals of the oncological consulting cabinet at the CRC yes☐ no☐

CRITERIA FOR THE DIAGNOSIS

1. Blood analyses (text) _____
2. Myelograms _____

2.1 Cytochemical analyses _____

3. Bone marrow biopsies _____
4. Patho-anatomical analyses _____
5. Immunological analyses _____
6. Lymphatic node biopsies _____
7. Cytogenetic analyses _____
8. Blood cell culture analyses _____
9. Hepatomegaly yes☐ no☐
10. Splenomegaly yes☐ no☐
11. Haemorrhagic syndrome yes☐ no☐
12. Lymphadenopathy yes☐ no☐
13. Articular syndrome yes☐ no☐
14. Other criteria _____

Medical comment_____

Fig A2.1. Verification Card for Leukaemia Cases

In some of the OODs, as in the Kaluga OOD, there is a medical out-patient card for each patient which contains further information such as the Notification of a cancer case diagnosed for the first time, epicrises of varying length on hospitalisation, results of blood analyses or bone marrow punctions, consultations of haematologists etc.

2ND LEVEL

Institution: Oblast Clinic (OC) or Oblast Paediatric Clinic (OPC)
Source: Medical History of the in-patient

Practically all leukaemia patients who were diagnosed at a rayon clinic come to the oblast out-patient department for further haematological consultation. In most cases, those patients then undergo treatment at the oblast clinic or the oblast paediatric clinic. An exception to this rule are patients with uncomplicated forms of CLL or CML with unequivocally established diagnoses and no need for hospitalisation.

The oblast clinics have, as a rule, specialized haematological departments as well as a consultant haematologist in the out-patient department. The in-patients' Medical Histories are kept in the archives of the OC, the Out-patient Cards in the registration offices of the out-patient departments. With help of the Medical histories, the following information is verified:

2.1. Surname, name, patronymic
2.2. Year of birth
2.3. Place of residence
2.4. Duration of hospitalisation
2.5. Full clinical diagnosis
2.6. Date of diagnosis
2.7. Anamnestic data and the results of diagnostic procedures that had been carried out in other medical institutions (Russian Haematological Research Centre, Russian Oncological Research Centre). Verified date of diagnosis
2.8. Clinical signs of leukaemia (hepato-splenomegaly, haemorrhagic syndrome, lymph node status, etc.)
2.9. Results of all blood analyses
2.10. Results of all bone marrow punctions
2.11. Other diagnostic procedures (bone marrow biopsies, lymph node biopsies, biochemical, immunological and cytogenetic analyses)
2.12. Autopsy-protocols

3RD LEVEL

Institution: Laboratories of the OC and the OPC
Source: Journal of Diagnostic Procedures

These journals are kept at the archives of the clinical laboratories at the oblast clinics. Results of the following procedures and analyses are recorded:

3.1. Myelograms
3.2. Cytochemical typing
3.3. Immunological typing
3.4. Cytogenetic typing

This information allowed to make the diagnosis more specific in several cases, thus ameliorating the level of verification.

4TH LEVEL

Institution: Laboratories of the OC and the OPC
Source: Archives of blood and bone marrow smears

4.1. Bone marrow smears, stained with standard methods
4.2. Blood and bone marrow smears which underwent cytochemical methods
    4.2.1. Myeloperoxidase
    4.2.2. Lipids
    4.2.3. PAS reaction against glycogen
    4.2.4. Unspecific esterase
    4.2.5. Acid phosphatase

The work with the morphological and cytochemical smears revealed some cases in which the morphological picture did not show a leukaemia, but e.g. a multiple myeloma, aplastic anaemia etc. Those cases had been added to the database at the stage of verification of the diagnosis, when the diagnosis was changed due to further analyses (repeated bone marrow punction, consultation of medical institutions in Moscow etc.). The same research was carried out for histological material (bone marrow biopsies, lymph node biopsies) and for the biopsies taken during autopsies at the patho-anatomical laboratories of the oblast clinics.

5TH LEVEL

Institution: All out-patient departments of the OC and the OPC
Source: Out-patient Card

The Out-patient Card contains information on further diagnosis as well as the treatment performed by the haematologist at the OC or the OPC

6TH LEVEL

Institution: Central Rayon Clinic (CRC)
Source: Out-patient Card

The most valuable source of information is the central rayon clinic, where the initial Out-patient Cards on all patients are kept. The Out-patient Card, as a rule, contains information from the first visit because of a haematological disease, such as all blood analyses, extracts from the medical histories after hospitalisation etc. The archives of the CRC also allowed the verification of the date and cause of death of deceased patients.

The ascertainment and verification on these six levels led to changes in the database, namely to the exclusion of cases in which the diagnosis *leukaemia* proved to be incorrect for various reasons.

72% (18) of all necessary changes (25) concerned chronic leukaemia, the vast majority of which were CLL. 50% (8 cases) of the cases recorded as CLL turned out to be Non-Hodgkin's lymphomas (200.1) after biopsy of lymphatic nodes. Indeed, CLL may be hard to distinguish from a differentiated lymphoma [COM 80, MIN 83]. 44% (7 cases) of CLL (204.1) were in reality multiple myelomas (203.0), but had been miscoded by the medical statistician when transferring the information from the Notification to the Control Card. The analysis of the medical histories, laboratory results, and myelograms supported the fact that there had been a technical mistake. This was confirmed by the verification of bone marrow smears within the framework of this study. Another case (6%) of CLL was also due to miscoding in the Control Card and the diagnosis was subsequently changed to lymphogranulomatosis (201). In one case, a miscoding error in the Control Card had led to the classification of a lymphatic metastasis (196.9) as leukaemia (208.9).

In 6 cases (24%) of the 25 cases in which the diagnosis could not be confirmed, various pathologies (anaemia (285), megaloblastic anaemia (281.0), death before diagnosis without autopsy (798.2)) were provisionally coded as acute leukaemia (208.0) in the Control Card. The diagnosis later remained unchanged in the Control Card, even though the revised diagnosis was unequivocal on the basis of the diagnostic procedures and had been changed in the medical histories. A list of all diagnoses changed is given in table 2.11 in the main text.

Table A2.1 gives the number of cases that were verified for the Bryansk and for the Kaluga oblasts with help of the various sources. It shows only those cases used for the epidemiological analysis (333), the 34 cases that were excluded on the basis of the verification were not taken into account.

In all cases that had occurred in the Bryansk oblast, a corresponding Control Card and in more than 40% of the cases, a Medical History was found. In some cases, even 3-5 Medical Histories could be allocated to one case if the patient had been treated repeatedly or in different in-patient institutions. Information from the diagnostic and pathological laboratories of the Bryansk oblast clinic and paediatric clinic was accessible in more than 30% of the cases.

Table A2.1 Sources for the verification of data in the Bryansk and the Kaluga oblasts

SOURCES FOR QUALITY CONTROL	Number of cases 1980 – 1998					
	Highly contaminated n=247		Slightly contaminated n=45		Control n=41	
	No	%	No	%	No	%
Notification or Control Card of the OOD	247	100	27	60.0	25	61.0
Out-patient Card (OODs, OCs, CRCs)	10	4.0	41	91.1	40	97.6
Medical History (OCs, OPCs, CRCs)	107	43.3	18	40.0	20	48.8
Histological archives of the CDL & PAL of the OCs*	73	29.5	21	46.7	12	29.3
Bone marrow smears	24	9.7	8	17.8	2	4.9
Blood analyses (text)	99	40.1	20	44.4	27	6.6
Bone marrow smears (text)	87	35.2	9	20.0	9	21.9
Cytochemical analyses	44	17.8	3	6.7	2	4.9
Immunol. / cytogen. tests	38	15.4	2	4.4	2	4.9
Clinical symptoms	74	29.9	10	22.2	8	19.5
Diagnosis was established at / in:						
Moscow	4	1.6	2	4.4	2	4.9
Oblast Clinic	122	49.4	37	82.3	32	78.0
City Clinic, Central Rayon Clinic	121	49.0	6	13.3	7	17.1

*Histological archives of the CDL & PAL of the BOC: journals of myelograms, patho-anatomical comments, results of lymphatic node biopsies

The verification of diagnoses in Kaluga was performed mainly on the grounds of the Out-patient Cards of the oncological dispensaries, the oblast clinic out-patients department and the central rayon clinics. In over 40 % of all cases, Medical Histories of hospitalised patients were consulted. Usually, patients would be diagnosed and treated in the specialized haematological departments of the Kaluga oblast clinic or paediatric clinic. In some cases, when the Medical History could not be found in the archives or was illegible (because of the physical conditions in the archives), the information was traced in the diagnostic and pathological laboratories of the Kaluga oblast clinic. Apart from that, all cases had been registered at the oncological cabinet of the central rayon clinic, were the *journals of newly diagnosed leukaemia cases* and *of deaths of cancer patients* were analysed.

Table A2.2 Leukaemia cases by subtypes and periods in the rayons under study (adults)

TYPE OF LEUKAEMIA	1980-1986						1987-1992						1993-1998						Total	
	Highly contam.		Slightly contam.		Control		Highly contam.		Slightly contam.		Control		Highly contam.		Slightly contam.		Control			
	No	%	No	%	No	%	No	%	No	%	No	%	No	%	No	%	No	%	No	%
ALL **204.0**	2	3.08	2	15.38	-	-	10	13.89	-	-	-	-	9	10.84	1	4.35	1	6.25	25	8.39
AML **205.0** / OAL **206.0, 207.0**	1	1.54	4	30.77	2	18.18	15	20.83	-	-	1	11.11	12	14.46	4	17.39	1	6.25	40	13.42
ALNOS **208.0**	13	20	2	15.38	2	18.18	8	11.11	1	16.67	-	-	3	3.61	-	-	-	-	29	9.73
ANL **208.0**	-	-	-	-	-	-	-	-	1	16.67	-	-	3	3.61	1	4.35	1	6.25	6	2.01
CLL **204.1**	13	20	1	7.69	6	54.55	23	31.94	2	33.33	4	44.44	31	37.35	11	47.83	7	43.75	98	32.89
CML **205.1** / OCL **205.8,207.1**	6	9.23	4	30.77	1	9.09	8	11.11	2	33.33	3	33.33	25	30.12	6	26.09	5	31.25	60	20.13
CLNOS **208.1**	12	18.46	-	-	-	-	6	8.33	-	-	-	-	-	-	-	-	-		18	6.04
LNOS **208.9**	18	27.69	-	-	-	-	2	2.78	-	-	1	11.11	-	-	-	-	1	6.25	22	7.38
Total 204.0-208.9	65	100	13	100	11	100	72	100	6	100	9	100	83	100	23	100	16	100	298	100

Table A2.3 Leukaemia cases by subtypes and periods in the rayons under study (children)

TYPE OF LEUKAEMIA	1980-1986						1987-1992						1993-1998						Total	
	Highly contam.		Slightly contam.		Control		Highly contam.		Slightly contam.		Control		Highly contam.		Slightly contam.		Control			
	No	%	No	%	No	%	No	%	No	%	No	%	No	%	No	%	No	%	No	%
ALL **204.0**	11	78.57	-	-	-	-	4	80	-	-	3	75	8	100	1	50	1	100	28	80
AML **205.0** / OAL **206.0, 207.0**	2	14.29	1	100	-	-	-	-	-	-	-	-	-	-	1	50	-	-	4	11.43
ALNOS **208.0**	1	7.14	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	1	2.86
CML **205.1** / OCL **205.8,207.1**	-	-	-	-	-	-	1	20	-	-	-	-	-	-	-	-	-	-	1	2.86
LNOS **208.9**	-	-	-	-	-	-	-	-	-	-	1	25	-	-	-	-	-	-	1	2.86
Total 204.0-208.9	14	100	1	100	0	0	5	100	0	0	4	100	8	100	2	100	1	100	35	100

Table A2.4 Leukaemia cases by subtypes and periods in the rayons under study (all cases)

TYPE OF LEUKAEMIA	1980-1986						1987-1992						1993-1998						Total	
	Highly contam.		Slightly contam.		Control		Highly contam.		Slightly contam.		Control		Highly contam.		Slightly contam.		Control			
	No	%	No	%	No	%	No	%	No	%	No	%	No	%	No	%	No	%	No	%
ALL **204.0**	13	16.46	2	14.29	-	-	14	18.18	-	-	3	23.08	17	18.68	2	8	2	11.76	53	15.92
AML **205.0** / OAL **206.0, 207.0**	3	3.80	5	35.71	2	18.18	15	19.48	-	-	1	7.69	12	13.19	5	20	1	5.88	44	13.21
ALNOS **208.0**	14	17.72	2	14.29	2	18.18	8	10.39	1	16.67	-	-	3	3.30	-	-	-	-	30	9.01
ANL **208.0**	-	-	-	-	-	-	-	-	1	16.67	-	-	3	3.30	1	4	1	5.88	6	1.80
CLL **204.1**	13	16.46	1	7.14	6	54.55	23	29.87	2	33.33	4	30.77	31	34.07	11	44	7	41.18	98	29.43
CML **205.1** / OCL **205.8, 207.1**	6	7.59	4	28.57	1	9.09	9	11.69	2	33.33	3	23.08	25	27.47	6	24	5	29.41	61	18.32
CLNOS **208.1**	12	15.19	-	-	-	-	6	7.79	-	-	-	-	-	-	-	-	-	-	18	5.41
LNOS **208.9**	18	22.78	-	-	-	-	2	2.60	-	-	2	15.38	-	-	-	-	1	5.88	23	6.91
Total 204.0-208.9	79	100	14	100	11	100	77	100	6	100	13	100	91	100	25	100	17	100	333	100

Table A2.5 Leukaemia cases by subtypes for the entire period (1980-1998) in the rayons under study (all cases)

TYPE OF LEUKAEMIA	Number of cases 1980-1998						Total	
	Highly contaminated		Slightly contaminated		Control			
	No	%	No	%	No	%	No	%
ALL **204.0**	44	17.81	4	8.89	5	12.20	53	15.9
AML **205.0** / OAL **206.0, 207.0**	30	12.15	10	22.22	4	9.76	44	13.2
ALNOS **208.0**	25	10.12	3	6.67	2	4.88	30	9.0
ANL **208.0**	3	1.21	2	4.44	1	2.44	6	1.8
CLL **204.1**	67	27.13	14	31.11	17	41.46	98	29.4
CML **205.1** / OCL **205.8,207.1**	40	16.19	12	26.67	9	21.95	61	18.4
CLNOS **208.1**	18	7.29	-	-	-	-	18	5.4
LNOS **208.9**	20	8.10	-	-	3	7.32	23	6.9
Total 204.0-208.9	247	100	45	100	41	100	333	100

Verification was difficult for various reasons

- In accordance with the official requirements, the clinical or even cytological type of leukaemia was often not given when the case was reported to the OOD.
- Diagnostic materials (blood and bone marrow smears), according to the regulations of the Russian Federation (and formerly the Soviet Union), only have to be stored for five years. The smears are not treated for conservation, as is the case for histological slides, so that the stain discolours and they become worthless for verification.
- Journals in which laboratory results (of bone marrow punctions and biopsies, lymphatic node biopsies, immunological etc. analyses) are recorded, are often stored for not more than five years.
- Many of the archives at the oblast, city and rayon clinics are insufficient for extended storage of papers, so that some of the initial medical documents could not be retrieved.
- The diagnostic process itself suffered from inadequacy to distinguish some types of leukaemia during the study period.

ANNEXE 3

CONFIRMATION - BESTÄTIGUNG

Ich erkläre hiermit, die vorliegende Dissertation am Medical Radiological Research Centre (MRRC) of the Russian Academy of Medical Sciences (RAMS), Obninsk, Russland, und am Strahlenbiologischen Institut der Ludwig-Maximilians Universität, München, Deutschland, selbständig angefertigt zu haben. Außer der angegebenen Hilfsmittel habe ich mich keiner weiteren Hilfsmittel bedient. Erkenntnisse, die aus dem Schrifttum ganz oder annähernd übernommen sind, habe ich als solche kenntlich gemacht und nach ihrer Herkunft unter Bezeichnung der Fundstelle einzeln nachgewiesen.

Die für die Dissertation verwendeten Daten wurden mir vom Direktor des MRRC RAMS, Professor VK Ivanov, zu diesem Zweck ausdrücklich zur Verfügung gestellt (siehe folgende Seite).

Ich habe bisher an keiner in- oder ausländischen Medizinischen Fakultät bzw. keinem Medizinischen Fachbereich ein Gesuch um Promotion eingereicht – weder über dieses, noch über ein anderes Thema.

Teile der vorgelegten Arbeit werden im Rahmen folgender Arbeiten veröffentlicht:

- Ivanov VK, Tsyb AF, Gorski AI, Nilova EV, Ivanova LV, Maksioutov MA, Khait SE, Becker SI, Kellerer AM (2003) Radiation-epidemiological analysis of leukaemia incidence among children and adolescents at exposure in the population of the Bryansk region after the Chernobyl accident. Eingereicht bei Environmental Radiat Biophys.

- Ivanov VK, Becker SI, Maksioutov MA, Bronsart von Schellendorff EV, Khait SYe, Korelo AM, Gorsky AI, Matjash VA, Vlasov OK, Kaidalov OV (2003) German-French Initiative for Chernobyl, Subproject 3.2.4. *Leukaemia Incidence among Children and Adults in the Most Highly Contaminated Territories of Russia*. Final Report.

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I entrust Susanne Isabel Becker with the data on leukaemia cases (1980-1998) in the Bryansk and Kaluga regions of Russia as well as with all relevant demographic and dosimetric information, which she may use at her discretion for her doctoral thesis.

Professor V. Ivanov
Corresponding Member of the RAMS
(Radiation Epidemiology)
Deputy Director of MRRC RAMS
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ACKNOWLEDGEMENTS

This study was conducted at the Radiobiological Institute of the University of Munich. I am obliged to the Director of the Institute, Professor Albrecht Kellerer.

My warmest thanks go to the two supervisors of this thesis:

Professor Viktor Konstantinovich Ivanov of the Medical Radiological Research Centre of the Russian Academy of Medical Sciences, Obninsk, Russia, who entrusted me with the data and was generous and supportive throughout the entire study period.

Professor Dieter Hölzel, Director of the Tumour Registry at the University of Munich, for his valuable suggestions and, above all, for helping me through a difficult time. This thesis may not have been written without his encouragement.

I would like to thank especially all the Russian colleagues involved in this project:

thank you for being such great colleagues and for having become friends in the course of the work. Your expertise, incessant enthusiasm and personal commitment was decisive for the quality of this study. I owe particular thanks to the responsible haematologist, Svetlana Yevgenevna Khait, the great data-processor, Aleksandr Mikhailovich Korelo, and the curator and wonderful organizer, Marat Adilievich Maksioutov.

I appreciate a lot the advice and often very practical help I have had all along from my colleague and friend, Elke Nekolla. Working with you is an experience that I would not like to miss. Thank you, Elke.

I am very grateful to Dr. Christine Waterhouse for haematological consultation and to my mother for meticulous proof-reading. I dread to think of the many mistakes that would otherwise still be in the text. Any remaining inaccuracies or mistakes are entirely my responsibility.

Last, but not least, my thanks go to friends and colleagues and to my father, all of whom provided anything from continuous support and helpful comments to the occasional kick.

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11/85 – 12/85 Lycée Vaugelas in Chambéry, France
1983 – 1984 The John Bentley School in Calne, Wiltshire, England (fourth form)

PROFESSIONAL ACTIVITIES

02/03 – date Weilheim Hospital, Department of General Surgery (Director: Prof. G. Hauer)

05/99 – 01/03 Research associate at the Radiobiological Institute at Ludwig-Maximilians-University, Munich (Director: Prof. A.M. Kellerer)
Epidemiological research: planning and organisational and scientific management of international multicentre studies on the health effects of the Chernobyl Nuclear Power Plant accident.

07/95 – 04/99 Student assistant at the Radiobiological Institute at Ludwig-Maximilians-University, Munich (Director: Prof. A.M. Kellerer)
Epidemiological research and planning of studies on the health effects of the Chernobyl Nuclear Power Plant accident, especially childhood leukaemia.

08/91 – 09/91 Journalistic work for Time Magazine, Moscow

06/89 – 07/90 Translating/interpreting and office work for Siemens AG, Moscow, Russia

PUBLICATIONS

Ivanov VK, Tsyb AF, Gorski AI, Nilova EV, Maksioutov MA, Khait SE, Becker SI, Kellerer AM (submitted in 2003) *Radiation-Epidemiological Analysis of Leukemia Incidence Among Children and Adolescents at Exposure in the Population of the Bryansk Region after the Chernobyl Accident*. Submitted for publication in Radiat Environ Biophys

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