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# ESTIMATION OF X RAY OVEREXPOSURE IN A CHILDHOOD LEUKAEMIA CLUSTER BY MEANS OF CHROMOSOME ABERRATION ANALYSIS

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**Abstract** — Only multiple X ray diagnostics could be identified as a common risk factor in a leukaemia cluster that appeared between 1985–1989 in the municipality of Sittensen in northern Germany. In order to judge if the effect could be explained by irradiation dose, estimates were done in two of the leukaemia cases and seven former patients of a practice where some of the leukaemia cases had been treated for orthopaedic reasons. The methods used for the reconstruction of doses were physical simulation and biological dosimetry by dicentric chromosomes in peripheral lymphocytes. Compared to the Bremen laboratory control the mean frequency of dicentric chromosomes in the lymphocytes of the seven volunteers was significantly elevated. An overexposure of about 12-fold could be derived compared to state of the art X raying. At least two cases of the leukaemia cluster in Sittensen can therefore be correlated to an overexposure by diagnostic X rays.



## INTRODUCTION

In Western Germany, all childhood malignancies have been registered since 1980. In a cluster analysis for leukaemia in the period 1983–1992, only a few significant elevations were observed in 8505 municipalities[1,2]. However, two locations showed an extreme deviation from the expected value by more than a factor of 7. While the highest rate was observed in the vicinity of a nuclear power plant[3], the second location, the municipality of Sittensen in northern Germany, is situated more than 40 km away from any nuclear installation.

The existence of a local cluster was first suspected by a teacher who had become aware of two leukaemia cases among the pupils of his school and a further one in his neighbours. Between 1985 and 1989 five cases of acute leukaemia had been diagnosed in children and one case in a 17 year old girl, as well as three other malignancies (Table 1).

The mean number of inhabitants $<15$ y of age in Sittensen for the related period is about 1600 and about 2300 for persons $<20$ y. The estimated incidences for acute leukaemia are given in Table 2. A reference period of 10 years was chosen in order to avoid a potential bias due to the case-driven (*a posteriori*) definition of the study period. The expected number of cases in the age of 0–14 y was derived from annual reports of the childhood cancer registry[4,5] and for young adults (15–19 y) from the annual reports 1980–1989 of the Federal State of Saarland cancer registry[6].

In 1990, the Ministry of Social Affairs of the Federal State of Lower Saxony established an expert committee to investigate the possible causes of leukaemia. The affected families were interviewed based on questionnaires in order to identify medical conditions, parental occupation, and toxic exposures in-doors and in the environment. They lived in different parts of the municipality which consists of several small former villages separated by distances of some kilometres. All families are old-established and had no contact with each other. Only two of the cases met in school or kindergarden.

Kindergardens as well as schools were examined for radon contamination, schools also for formaldehyde, xylene, toluene, and benzene. The industrial activities in that region were considered, but unusual exposures were not observed[7]. However, with the exception of one, a 10 months old child with unknown exposure history (case no 1), all patients had undergone repeated X raying, most of them at a very young age (see Table 3).

Three of the children (Table 3) had been patients of the same orthopaedic practice (nos 3, 5, 6) in Rotenburg which is the county town at about 20 km distance to Sittensen. Although X ray diagnostics is a known risk factor for leukaemia[8,9] the expert committee doubted

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that state of the art investigations could be responsible for the observed high effect.

In 1991, it was therefore decided to examine the exposure conditions in that practice. The X ray machine had been installed in 1975 and technical supervision had attested undisturbed function in 1977 and 1990. Unfortunately, it was not possible to inspect the apparatus because the physician had died and the machine had been replaced.

The ministry ordered an evaluation of the quality of X raying by the orthopaedist, which was done by checking the films of 20 patients in a random sample. The inspecting experts attested a general overexposure compared to the usual standard at that time, generated on the one hand by technical insufficiencies (inadequate film–foil combination, exhausted developer, overexposure of the film, partly lack of beam collimation and shielding of the gonads). On the other hand, an exceptional high frequency of films per patient was found, the indication for X raying at all was doubted in several cases, and much too high a rate of repeated checks for the same diagnosis was stated.

In order to obtain further information about the real doses in that practice the following methods were applied.

## MATERIALS AND METHODS

Two kinds of retrospective dose investigations were undertaken. First, because it is known from the literature that the doses received from the same kind of X ray investigation in paediatric situations differ by one to two orders of magnitude[10], the physical conditions were simulated retrospectively for the individual cases. This was possible for the patients nos 3 and 6 (Table 3), because the X ray films as well as patient documentation were still available. The documents of the third patient of the orthopaedic practice (no 5 in Table 3) had not been stored.

The cases 2 and 4 had been diagnosed in other practices and were not followed up because the number of films was not known.

The leukaemia patients 3 and 6 (Table 3) had died before this investigation. Therefore only a physical dose reconstruction could be done. The leukaemia patients, however, were not suitable for biological dosimetry in general, because they had been treated by cytostatic therapy and/or brain irradiation.

An additional dose estimation using chromosome aberrations was carried out in a sample of healthy volunteers who had been patients of the same orthopaedic practice. Dicentric chromosomes and centric rings in peripheral lymphocytes are known as highly specific indicators for radiation[11]. The aim was to compare the results with the physically derived dose estimates in order to assess quantitatively the assumed overexposure due to incorrect operating of the X ray machine and as a consequence of poor film development.

The ages of the seven former patients of the orthopaedic practice had been between 3 months and 14 years at time of the exposure. They were selected because they had undergone a high number of X rays (Table 4) and were investigated for chromosome aberrations in 1991 and 1992.

**Table 2. Incidence density of acute leukaemias in Sittensen, 1980–1989.**

| Age group | Observed | Expected | SIR | 95% CI– | 95% CI+ |
|---|---|---|---|---|---|
| <15 | 5 | 0.68 | 7.4 | 3.1 | 17.8 |
| <20 | 6 | 0.86 | 7.0 | 3.1 | 15.6 |

SIR Standardised incidence rate.
SIR in 4 and 5 age groups, respectively (<1 y, 1–4 y, 5–9 y, 10–14 y, 15–19 y); SIR calculated using an extension of the incidence density rate command in Stata (StatCorp.Stata Statistical Software: release 4.0 College Station, TX: Stata Corp).

**Table 1. Leukaemia in children and one juvenile and other malignancies in children of Sittensen.**

| Disease | No | Sex | Date of birth | Diagnosis | Date of diagnosis | Age at diagnosis |
|---|---|---|---|---|---|---|
| Leukaemia | 1 | F | 7/1984 | ALL | 5/1985 | 0 |
| | 2 | M | 4/1983 | ALL | 1/1987 | 3 |
| | 3 | M | 6/1980 | T-ALL | 1/1988 | 7 |
| | 4 | F | 12/1975 | ALL | 8/1988 | 12 |
| | 5 | F | 5/1976 | AML | 6/1989 | 13 |
| | 6 | F | 11/1972 | ALL | 11/1989 | 17 |
| Other malignancies | 7 | M | 6/1982 | Wilm's tumour | 8/1985 | 3 |
| | 8 | F | 5/1971 | Rabdomyosarcoma | 2/1987 | 15 |
| | 9 | M | 9/1973 | M. Hodgkin | 11/1987 | 14 |

ALL: Acute lymphoblastic leukaemia; T-ALL; T-cell type of ALL; AML: acute myeloid leukaemia.

### Physical dose simulation

The exposure conditions were reconstructed based on X ray documentation cards of the two leukaemia cases and of those from each volunteer. An X ray machine of the same type as the one used for the original radiographs was used to expose acrylic plastic patient phantoms individually adjusted to represent the patient's thickness.

The kind of examination — the body section and the beam direction — was derived from the radiographs. The exposure field was also estimated from the films. On all images no beam collimation was visible, therefore the value of the film format was taken as the value of the imaging field. The voltage used, filtration (2.5 mm Al) and screen–film combination could be abstracted from the patient's documentation. The thickness of the body of the children was quoted from exposure tables for standardised radiographs for infants and children[12]. The values of the focus–film distance were selected from typical data published by the manufacturer of the X ray machine (Siemens) and elsewhere[12].

The skin doses were measured with thermoluminescence dosemeters (TLD rods, 1 mm diam. x 6 mm, lithium fluoride). As TLD reader a commercial instrument was used (model 4000, Harshaw). During readout of the dosemeters a continuous gas flow (0.5 $l.min^{-1}$) was used to avoid surface area effects. Since the response of the TLD is affected by their previous radiation history and thermal history, the material must be suitably annealed. The conditioning of the TLD was made by the method of Cameron[13].

The TLD were calibrated in the non-shielded beam of an X ray unit using voltages of 45–75 kV by comparison with a calibrated diagnostic dosemeter (DALi, PTW). The standard deviation of the conversion factor $K_f$ = absorbed dose/Tl response was 2.3% of the mean value. The minimum detectable dose was estimated to be 24 μGy.

From the skin dose the exposure (free-in-air) was evaluated by means of backscatter factors[14]. From these values the mean active bone marrow dose was calculated for each radiograph of the leukaemia patients and the whole body dose of the volunteers by the tables and parameters of the NCRP Report No 68[15]. The whole body dose — i.e. the dose average in the whole

**Table 3. Leukaemia cases with known history of X rays in Sittensen.**

| X rays | | | | | Leukaemia | | | |
|---|---|---|---|---|---|---|---|---|
| Age of exposure | No | Period | Number | Because of | Year of diagnosis | Age at diagnosis | Latency * | Type |
| 0.3–1.5 y | 3 | 1980–1982 | 8 | hip dysplasia | 1988 | 7 | 5.8 y | T-ALL |
| 0.5–1 y | 2 | 1983–1984 | unknown | hip dysplasia | 1987 | 3 | 3 y | ALL |
| 1.5/9 y | 4 | 1977/1985 | unknown | fractures | 1988 | 12 | 6.5 y | ALL |
| 2 y | 5 | 1977 | unknown | hip dysplasia | 1989 | 13 | 11 y | AML |
| 5–13 y | 6 | 1977–1986 | 16 | scoliosis | 1989 | 17 | 5.2 y | ALL |

*Mean period between exposure and leukaemia diagnosis.

**Table 4. Physically estimated mean whole body dose and chromosome aberration analysis in seven young volunteers.**

| | Age at time of the investigation | Number of films | Sex | X rayed in the age | Type of diagnosis | Physically estimated dose (mGy) | Number of cells | Number of dic+cr | Yield of dic+cr $\times 10^{-3}$ |
|---|---|---|---|---|---|---|---|---|---|
| A | 13 | 20 | f | 9–12 | spine | 19.3 | 1710 | 11* | 6.4 |
| B | 18 | 9 | f | 6; 14 | spine/pelvis | 8.2 | 1042 | 3 | 2.9 |
| C | 13 | 11 | m | 8; 10 | spine/pelvis | 10.1 | 1026 | 2 | 1.9 |
| D | 10 | 7 | f | 0–4 | spine/pelvis | 1.7 | 1024 | 0 | 0 |
| E | 8 | 10 | m | 0–6 | pelvis a.p. | 1.9 | 1071 | 1 | 0.93 |
| F | 8 | 14 | f | 0–7 | spine/pelvis | 3.1 | 1002 | 0 | 0 |
| G | 6 | 8 | m | 0–4 | spine, pelvis knee, shoulder | 1.3 | 1002 | 1 | 1.0 |
| | | | | | | | Σ 7877 | 18** | $2.3 \pm 0.5$ |

*1 tricentric chromosome was found which was counted as 2 dic equivalents.
**Only one centric ring was found in the whole sample (volunteer B).

body — was needed for comparison with the dose response of chromosome aberrations in the whole system.

### Biological dose estimation by chromosome aberration analysis

Heparinised blood samples, 1–5 ml, were drawn by venipuncture. Lymphocyte cultures and slide preparation have been described elsewhere[16]. The metaphase finding was facilitated by a semi-automatic computerised system which included a data management tool (Metaphasefinder, MetaSystems, Altlussheim, Germany).

At least three experienced scorers were advised to analyse about 335 first division metaphases from each donor, if possible, and to score for every kind of structural aberration. The dicentric and centric ring chromosomes were used as indicators for the mean whole body radiation exposure (Table 4).

### Estimation of the 'probability of causation' by radiation for individual leukaemia cases

In order to judge the probability of causation by X rays for the observed leukaemia cluster by comparison with known induction rates in exposed humans the collective dose in the population of Sittensen must be known. It was, however, not possible for reasons of personal data protection even to get an overview about the number of patients and the total number of films in the orthopaedic practice. Our experimental findings could therefore only be used to derive individual estimates for the two patients with the known number of films after the method developed for the tables on the 'probability of causation'[17].

A doubling dose for leukaemia in childhood of 27 mGy can be derived from the modelling of the BEIR committee[18] which shows a relative risk of 4.66/0.1Gy for children of the age of 5 at exposure, lasting for a period of 2–15 years after that. This value is based on the findings in the Japanese A bomb survivors. Because the RBE is energy dependent also for low LET radiation it should be considered that 66% of the exposure in Hiroshima and Nagasaki was caused by very high energetic γ radiation above 500 keV, and 30% between 750 keV and 12 MeV[19]. Because the LET declines considerably with the energy above 150 keV[20,21] it seems to be appropriate to assume a quality factor of 0.5 for the Japanese exposure. This results in a leukaemia doubling dose of 13.5 mSv for X rays in children.

Using the Japanese data[22] as probability distribution for the appearance of leukaemia after exposure in childhood (Figure 1) three cases of the Sittensen cluster, including the two with a known number of films, will be found in the maximum of the curve (latency period see Table 3). The mean relative risk RR(t) can be set to 1 assuming that if a leukaemia develops it will occur within 17 years after irradiation. The probability p that the disease is induced by X ray exposure rather than by spontaneous occurrence is then given by

$$p = \frac{RR(t)D_{exp}}{RR(t)D_{exp} + D_2} \quad (1)$$

where t is the time after irradiation, $D_2$ the doubling dose for childhood leukaemia and $D_{exp}$ the bone marrow exposure of the person. RR(t) = 2.5 can be derived from Figure 1 for the case no 3 (latency 5.8 y) and RR(t) = 2.2 for the case no 6 (latency 5.2 y).

## RESULTS

The physically estimated dose for the leukaemia cases 3 and 6 (Table 3) resulted in values of 0.5 mGy and 9.0 mGy for the red bone marrow. These low doses, in spite of the high number of films, are obtained because the proportion of red bone marrow in the exposed field was rather low. The uncertainty of these estimates of a 'state of the art' exposure is dominated by the unknown possible deviation of the assumed portion of bone marrow in the exposure field. We assume that these estimates may be valid within a factor of two.

Using biological dosimetry it is generally accepted that the whole body dose in cases of nearly homogeneous irradiation will represent the dose of the peripheral lymphocytes. The volunteers had been X rayed in a rather large part of their bodies, therefore the estimate of the mean dose in the whole body from the irradiated volume may also be a valid measure for the lymphocytes. A greater thickness of the examined body of about 4 cm compared to the age-dependent phantom used in the NCRP tables[15], however, will double the dose. We therefore estimate that the physically simulated dose value for the volunteers is correct within 50% of deviation.

The physically derived doses for the seven volunteers are shown in Table 4. They are compared to the measured frequency of dicentric chromosomes (dic) and centric rings (cr) in these persons.

A linear regression analysis was carried out between physical dose estimate and aberration frequency because the dose–response for dic+cr has been found to be linear in the low dose region up to about 500 mGy[23]. The analysis (see Figure 2) results in an equation $y = 3.20 \times 10^{-4}x - 2.10 \times 10^{-4}$ where y is the number of dic+cr per cell and x the dose in mGy. The correlation coefficient is 0.94.

The background frequency derived by extrapolation to zero dose results in a value of $-0.21 \times 10^{-3}$ and does not deviate significantly from the Bremen adult laboratory control value[24] of $(0.46 \pm 0.15) \times 10^{-3}$. It is to be compared to patient B in Table 4 because she was adult at time of the chromosome study. Later measurements of the background frequency in children resulted in a considerably lower frequency of $(0.10 \pm 0.10) \times 10^{-3}$ than found in adults[25].

Assuming a homogenous distribution of the lymphocytes in the whole body the rate of dic+cr represents a dose which can be derived using *in vitro* calibration experiments. The dose response in venous blood of adults and children resulted in equal aberration rates[26]. The linear dose coefficient for X rays which was derived from measurements of several authors is $(0.521 \pm 0.026) \times 10^{-4}$ mGy[11], i.e. an about 6-fold higher aberration response was found in the diagnosed volunteers than would be predicted by the physical dose estimate.

## DISCUSSION

The derived overexposure of patients in the orthopaedic practice must be considered as a minimum estimate because dic are unstable aberrations. Their decline

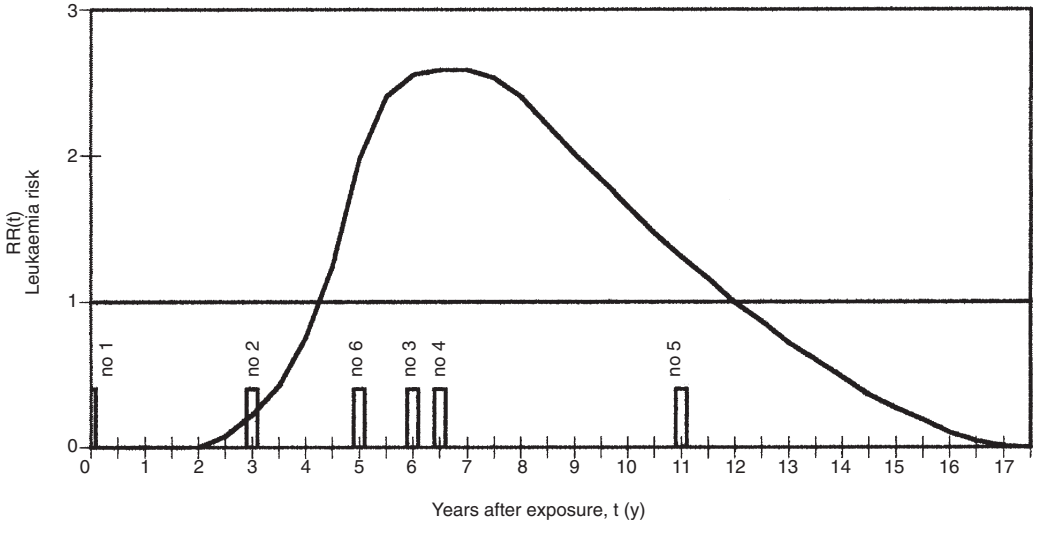


Figure 1. Latency distribution RR(t) for leukaemia in children <15 y at exposure of the Hiroshima sample and leukaemia appearance for the cases in Sittensen (mean time between X ray exposures and diagnosis); the exposure of case no 1 (<1 y of age) is unknown.

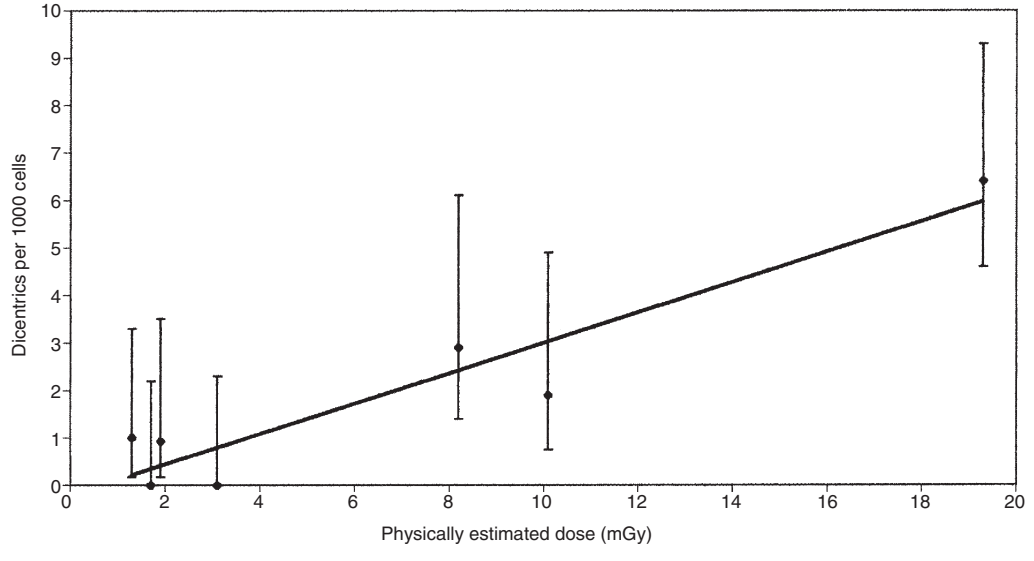


Figure 2. Physically estimated dose and response for dicentric aberrations and centric rings in seven former patients of an orthopaedic practice. $y = 0.3201x - 0.2096$, $R^2 = 0.8901$, $r = 0.94$.

in children with time, however, is not known. If one assumes that it will be not less than in adults a loss of at least 50% will occur in the first 2 years after exposure which corresponds to the mean delay between exposure and aberration analysis in the seven volunteers (Table 4). Consideration of the decline therefore leads to an overexposure of about 12-fold measured by the dic rate.

The bone marrow dose for case no 3 in Table 3 with a physically derived value of 0.5 mSv which corresponds to 6 mSv assuming the derived 12-fold overexposure would therefore — corresponding to Equation 1 — result in an induction probability for leukaemia by X ray exposure of 53%.

For the second case with a known number of films (no 6 in Table 3) and a physically derived bone marrow dose of 9.0 mSv corresponding to108 mSv considering overexposure a probability of 95% for leukaemia occurence by irradiation is obtained.

The assumed association between X raying and leukaemia induction in Sittensen is also confirmed by the fact that the rate of other malignancies than leukaemia in children was also significantly elevated. While the three cases described in Table 1 were registered by ourselves the German registry for childhood cancer listed four other malignancies against 1.5 expected ones[2], three of them were soft tissue tumours diagnosed between 1987 and 1992 and one case of a nephroblastoma occured in about 1985. The efforts of the ministry and the expert committee had, however, been focused exclusively to the leukaemia cases.

Assuming the derived doubling dose of 13.5 mSv for leukaemia and the 7.4-fold increase (Table 2) a causation of the whole cluster by X rays would need a mean dose for the children in Sittensen of 99.9 mSv in 10 years, i.e. about 10 mSv bone marrow dose in every child per year for a period of 10 years which appears to be too high. It must, however, be considered that a situation of medical overcare and exposure in a region would extend possibly also to the parents of children. The doubling dose for leukaemia in children after prenatal exposure is only about 5 mSv[27]. The findings about preconceptional induction by the exposure of fathers and mothers also suggest low doubling doses of only a few mSv[9,28,29].

Furthermore it was registered for Western Germany in the year 1978 that every 4th male suckling was X rayed for hip dysplasia prevention[30]. Sittensen may have been a stronghold of such investigations in the 1980s. Related documents, however, were not available in that region.

The question of causation for the Sittensen leukaemias was further clarified by the mentioned case–control study on the causes for leukaemia in children of Lower Saxony[2]. The authors included the Sittensen cases and derived the highest risk factor for diagnostic X raying. Children who were X rayed more than four times showed a relative risk of 6.96 for acute leukaemia compared to control cases from Sittensen ($p = 0.04$). Other considered risk factors in the study — mainly parameters concerning immunological reactions — showed far lower values. Although the authors did not draw this conclusion[2] their case–control results support that diagnostic X rays may have contributed significantly to the leukaemia cluster in Sittensen.

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