Dose-Effect Considerations for Childhood Leukaemia in Populations with Repeated Low Dose Exposures

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Introduction

In the case of the reported leukaemia cluster and increase in the whole population near the nuclear power station Krümmel [5, 12, 21] it was stated by the officials that the radioactive releases of the reactor - even if occasionally above legal limits - would never explain the effect, because the dose would have been much too low. This well-known argument, however, becomes increasingly questionable because of a repeated evidence of effects in the neighbourhood of those installations which are at least potential sources of an agent proven many times for causation of malignancies.

Our own experience was already based on two former investigations on leukaemia elevations in Germany, where we also ascertained relevant overexposure in the concerned population by biological dosimetry. The first one occured in the vicinity of a former uranium processing plant [10, 11], the second one showed X-raying for diagnostic purposes as a common risk factor of cases. Using conventional risk factors for radiaton-induced leukaemia in these situations there seemed to be a considerable gap between the extent of the observed effect and the possibly reached dose.

„Accepted" risk factors for leukaemia are derived from the Japanese A-bomb survivors and may not be valid for situations of chronical low dose exposure for several reasons [16, 25]. Up to now it was not possible to derive a reliable estimate of the collective bone marrow dose in populations living in a contaminated area and compare it to an observed leukaemia elevation. It is, however, known from the literature that diagnostic X-rays - even in modern times - have caused leukaemia to a measurable degree [4, 7, 18, 24]. In these situations there also exists a missing link between the possible exposure and the prognosticated effect. Although the real doses are also widely unknown it is easier here to get an estimation about the range of exposures and the degree of underestimation by conventional view.

Doubling dose for leukaemia induction by diagnostic X-rays from the Los Angeles study

The highest relative excess risk for leukeamia which was derived by Preston-Martin and coworkers in their case-control study was 0.76 per cGy, which leads to a doubling dose of 13 mGy [18]. This was however for adults. These were found to be less sensitive compared to children up to the age of 10 by a factor of 4.7 in the A-bomb survivors [22], which would mean a doubling dose for children of only 2.8 mGy.

The BEIR V-committee [3] developed an age-dependent risk model for leukaemia, based on the Japanese data, which leads to a doubling dose of 27 mSv for children exposed in the age of 5. The discrepancy to the derived value from diagnostics - by a factor of 9.6 - is evidently not completely explainable by a recall bias in the X-ray study which is discussed by the authors. One of the common deficits in deriving risk factors from the A-bomb survivors is to neglect the different qualities of low LET radiation. The energies of the γ-rays delivered by the A-bombs are extremely high compared to conventional exposures, lying predominantly in the range 2-5 MeV [27].

Taking the induction of dicentric chromosomes in lymphocytes as a reference for stochastic effects Straume derives an increase of effectiveness for 250 kV X-rays of 4 and for the diagnostic range of about 80 kV a factor of 4.3 [27].

If one therefore reduces the BEIR estimate by considering this difference the doubling dose for leukaemia in childhood is lowered to 6.8 mSv. It was moreover pointed out by the BEIR committee that the Hiroshima research institute began to work in 1950 and therefore the leukaemia cases in the first 5 years were not completely registered. In order to consider this for children we refer to the collectives which were irradiated because of ringworm of the scalp [1, 18]. In these the maximum rate of leukaemia appeared after 4 years und 50% of cases occured within this period. Assuming 50% misrecording for the young A-bomb survivors the above derived value for the doubling dose will be lowered to 3.4 mSv. This figure is consistent with the findings in Los Angeles because there may, indeed, be some underestimation of the number of films by the patients who were interviewed. In addition to this the dose estimation assumed optimal techniques for each exam.

Leukaemia cluster in children of Sittensen, Germany, and evidence of overexposure by X-raying

5 cases of leukaemia and 3 cases of other malignancies in children, additionally 1 case of leukaemia in a young adult, were diagnosed between 1985 and 1989 in Sittensen, which is a village of about 8000 inhabitants in the northern part of Germany between the cities of Bremen and Hamburg. The expected value for leukaemia in children in 10 years of observation would have been 0.68 case after the tumour registry for children which is conducted since 1980 in Western Germany and shows a mean rate of 4.3 10^{-5} a^{-1} [9]. A reference time of 10 years is chosen because of the known latency distributions after postnatal [3] and prenatal [26] exposure. The elevation of leukaemia in children then reached a factor of 7.4.

5 of the observed 9 malignancies were investigated by questionnaire in the families including health histories of children and parents as well as exposures by chemical agents or radiation. There was found only one common risk factor: all of the cases had been X-rayed several fold, 3 of them in a very early age because of hip dysplasia (Table 1).

3 of the cases had been patients of the same orthopediatric practise. Because it is known from the literature that the exposures for

Table 1: Leukaemia cases with known history of X-rays in Sittensen

				X-rays	Leukaemia		
No.	in the age of (y)	period	number	because of	year of diagnosis	age at diagnosis	type
1	0.3-1.5	1980-1982	8	hip dysplasia	1987	6	ALL
2	0.5-1	1983-1984		hip dysplasia	1987	3	ALL
3	2	1977		hip dysplasia	1988	12	AML
4	1.5/9	1977/1985		fractures	1989	12	ALL
5	5-13	1977-1986	16	scoliosis	1989	16	ALL

the same kind of X-ray investigation in paediatric situations differed up to factors of 40 [17] we tried to reconstruct the conditions in that practise which was known already for exceptionally high frequencies of films per patient. Because of legal restrictions it was impossible to find out the number of Sittensen patients there. It was also not possible to investigate the X-ray machine, because the physician had died in 1991 and the apparatus was eliminated.

The exposure of children in the orthopediatric practise occured with energies in the range of 40-75 kV, therefore the factor from Straume is somehow higher than formerly considered (4.5) and the doubling dose is 3.0 mSv. This would mean that 3 excess cases in Sittensen caused by the suspicious practise would demand a mean bone marrow dose of 13.3 mSv in 1600 children of Sittensen or a collective dose of 21.2 Sv, which remains to be incredibly high.

The efforts to illuminate the problem based on voluntary cooperation of patients and the successor of the physician, and consisted of 1) evaluation of the X-rays in the leukaemia patients, 2) reconstruction of patient exposure by phantom studies with an X-ray machine of the same type, 3) biological dosimetry in former patients of the orthopediatric practise, 4) quality evaluation of former X-rays of this practise.

Cases No.1 and No. 5 in table 1 were patients of the practise where the X-ray films were available, the documents of the third patient (No.3) had been eliminated after 10 years of storage. The documented high frequency in the others supported the suspicion, also the observed periods between exposure and diagnosis of about 6, 3.5 and 7 years. The estimated accumulated bone marrow doses derived by physical simulation, however, were only 0.5 and 9 mSv in these patients.

It could be shown by biological dosimetry in former patients with available X-ray documents that a severe overexposure had occured. The rate of dicentric chromosomes of 7 volunteers in the age between 5-18 years is compared in fig.1 to the doses estimated by physical simulation refering to the X-ray films. Considering the delay between exposure and blood investigation and assuming a half life of dicentrics of 1.5 years, the original mean rate of dicentrics in this study resulted in 6.6 10^{-4}/D where D is the physically derived bone marrow dose in mGy.

In contrast to this, the calibration factor for Co 60 irradiation is 1.79 10^{-5} dics per mGy, corrected by the factor of 2.8 for higher effectiveness of the diagnostic X-rays after Straume this results in 5.02 10^{-5} dics per mSv. Therefore the overexposure compared to the physical dose estimation is 13 fold. The overexposure in this practise was confirmed by evaluation of the quality of films which was extremely bad for the most part.

If this is considered using a factor of 13 the assumed causative exposure by this practise would correspond to a regular mean dose in 1600 children of 1.0 mSv and a collective dose of 1.6 Sv. Such an exposure of a local population appears to be possible considering the fact that in the late 70ies about 25 % of all German sucklings were X-rayed for prevention of hip dysplasia [28] and that this special physician used to order many films for the same patient and the same disease. The causative role of X-rays in the Sittensen cluster was further confirmed by a case-control study which was done in 2 districts of Lower Saxony including the Sittensen cases [13]. The authors found a 7-fold significant elevation of leukaemias in children who had been X-rayed more than 4-fold compared with a local control.

From the case-control study can be concluded that part of the leukaemia cluster in Sittensen may have been induced by prenatal exposure of the children and preconceptional exposure of the parents. Although such

an influence will exist it can be concluded from the observed effects for diagnostic X-rays that the doubling dose for leukaemia in children will not be much higher than 3 mSv.

Conclusions for leukaemia induction in populations by radioactive contaminations

In situations of chronical exposure by radioactivity the difference in effectiveness against the high energetic gammas in Hiroshima and Nagasaki may be less dramatic than in the case of soft X-rays. If we assume a RBW like that of 250 kV the doubling dose for postnatal exposure of children would be 3.4 mSv. But in contrast to single exposures where these stages can be neglected because of too short phases of sensitivity, the other possible pathways for induction of malignancies in a population should be considered, i.e. the exposure of the unborns and of fathers and mothers before conception.

A stable population of about 1600 children as has to be considered in the example of the cluster in the proximity of the nuclear power plant Krümmel requires 107 successful pregnancies per year resulting in 80 prenatal person years at risk. This has to be compared to 1600 person-years of possible postnatal exposure of individuals under the age of 15. A doubling dose of 3.3 mSv for leukaemia after prenatal exposure is derived by using the data of the Oxford Survey of Childhood Cancers [8], which is in some conflict compared to the above derived 3.0 mSv for postnatal X-ray exposure because the fetus is thought to be more sensitive. But in the over all range of uncertainties this may remain tolerable. This would then mean that the additional contribution of the prenatal exposure in such population to the postnatal effect would be only about 80/1600 = 5 % which can be neglected for this rather raw estimate.

This is also true for preconceptional exposures. Although, in our opinion, the genetic induction shown by Gardner [6] is real, because it was found already in former studies on animals [15] and in several investigations after X-ray diagnostics of fathers and mothers, the resulting effect will remain neglectable in stable or decreasing populations. This is because the sensitive phases lie directly before conception and therefore the duration of these phases is short.

In order to estimate the doubling dose for genetic induction of leukaemia via exposure of the father we refer to the data of Gardner et al. [6] who found a 2.4fold increase for this effect (mean for the different controls chosen). Although in our opinion the postmeiotic phase of spermatogenesis should be considered which lasts about 74 days [2], Gardner et al. were assuming a period of 6 months before conception as the time of risk. The mean dose in 6 months for employees of Sellafield was determined to be 5 mSv from [14]. This leads to a doubling dose of 3.6 mSv and 53.5 person years at risk compared to 1600 in the postnatal state.

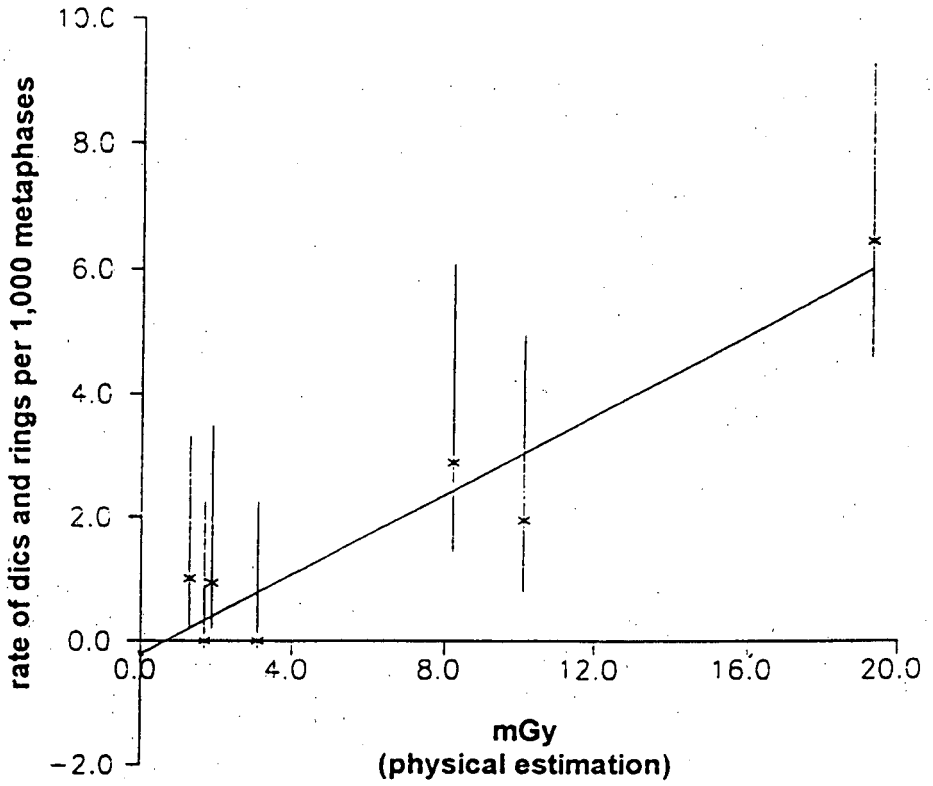
For induction of leukaemia by exposure of the mother we refer to the results of Shiono et al. [23] because - in contrast to other authors - they carried out a prospective study. The most sensitive phase for oozytes is considered to exist immediately before ovulation, i.e. before conception. The relative risk in the study, however, is not derived separately for leukaemia but only for all malignancies in childhood. The refered rate was doubled by us in contrast to their given RR of 2.61 because they investigated only children up to the age of 7 years. The mean gonadal dose by X-ray exposure is assumed to be 3 mSv which results in a doubling dose of 1.4 mSv. With 107 pregnancies per year in the community of Elbmarsch an overall preconceptual period of 26.7 years is derived, by assuming that

these mothers are not pregnant for 3 months of the year.
Compared to the somatic effect and accepting the low doubling dose as derived all the exposures of the parents will contribute less than 15 % of the effects in a stable or decreasing population.

Conclusions for nuclear power plant emissions

Dose-response relations from diagnostic X-rays show that the „accepted" risk factors for leukaemia underestimate the effects in low dose situations at least about 8-fold. This can be explained in a quite conventional manner by two facts: 1) the missing registration of cases in the first years after the explosions in Hiroshima and Nagasaki, 2) the different qualities of the compared low LET radiations. Inverse dose rate effects and supralinear dose-dependencies which were found by several authors for experimental end-points could, moreover, lead to even higher leukaemia rates per dose.
The derived doubling dose of about 3 mSv refers to children in the age of 5 at exposure. Further efforts should be made for developing an age dependent risk estimatte because this would be moreadaequate for exposures of populations. With a doubling dose of 3 mSv the somatic effect will be predominant in such populations if they are stable or of decreasing regeneration. For the cluster in the proximity of the nuclear power plant Krümmel we observe an effect in children which is 8.7-fold (6 cases related to 16.000 person years).
Because of the contaminations we have observed in the surroundings of Krümmel [20] we have concluded that the main contribution to the bone marrow dose occured by ingestion of ß-emitting bone seekers. We therefore assume an elevated RBE and a doubling dose of 3 mSv. The effect would be explained thus by a mean bone marrow dose of 26 mSv. This is rather high compared to the German dose limit of 0.3 mSv per year and would demand a more than 10-fold overexposure in the case of chronical leakages, but seems to be not impossible so far after our investigations.

Fig. 1: Biological dosimetry in 7 patients of the orthopediatric practice, Sittensen, Northern Germany



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