Assessment of Radiation Exposure by Analysing Unstable Chromosome Aberrations

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Introduction

Chromosome dosimetry based on the registration of unstable aberrations dates back to 1962, when Bender and Gooch for the first time carried out dose assessments on three individuals who had been accidently exposed to ionising radiation at Hanford, one of the largest atomic plants in the United States [8]. In 1982 a Research Programme on the „Use of Chromosome Aberration Analysis in Radiation Protection" was initiated by the International Atomic Energy Agency (IAEA). The main purpose of this project was to establish the method of chromosome aberration analysis for dose assessment as a complement to the routine physical dosimetry [34]. Over the last 30 years the method has been increasingly improved upon and is now the most widespread and reliable biological technique for retrospective dose estimation in high- as well as low-dose ranges [7,10,22,32].

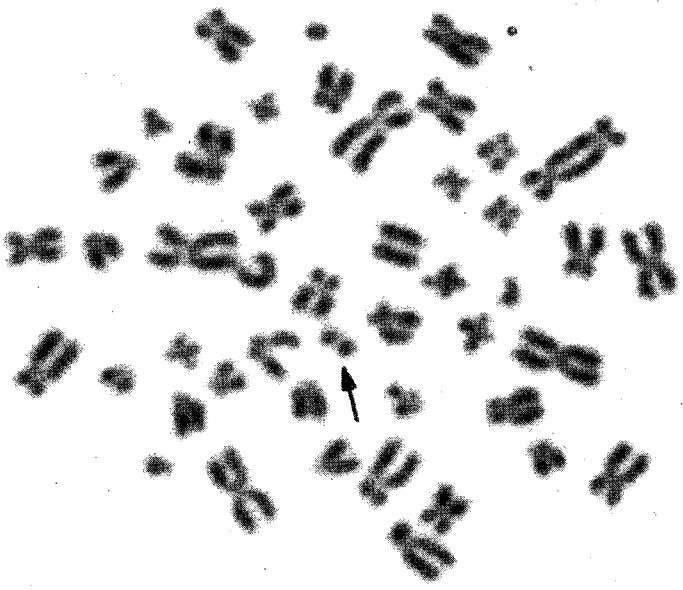
In the past chromosome aberration analysis was mostly used for dose assessment in cases of occupational radiation exposure, particularly when there were difficulties in interpreting the data or physical dosemeters had not been worn [2,9,26,30,55]. The method was likewise applied for patients who had been exceptionally exposed to ionising radiation during medical treatment [59] and in addition it was used in cases of claims for compensation for radiation injuries following exposures of the public to radioactive releases from nuclear installations and after nuclear weapon tests or from reactor accidents like Chernobyl or Three Mile Island [6,14,42,64].

Chromosomal aberrations

Chromosome analysis is performed in human peripheral T-lymphocytes, a cell population which is predominantly in a non-dividing DNA pre-synthetic stage of the cell-cycle. For this reason radiation-induced chromosomal breakages are fixed in the genome of these interphase cells and can be used as a „biological dosimeter". In vivo T-lymphocytes only proliferate when they are presented with an appropriate antigen. In vitro antigen-induced proliferation can be achieved by cultivation in the presence of certain plant lectins, predominantly Phytohaem-agglutinin (PHA). In vitro stimulation was the breakthrough which made peripheral lymphocyte chromosomes accessible for cytogenetic analysis using transmission light microscopes [44].

Among the various types of radiation-induced chromosomal aberrations, for an assessment of radiation exposure usually the dicentric chromosome (dic) and additionally the centric-ring chromosome (cr) are used for quantitative analysis. Dicentrics have two centromeres, they originate from two breaks in two chromosomes which fuse together. In a first in vitro metaphase a dicentric chromosome will be generally accompanied by an acentric fragment (Fig. 1). Rings develop from two breaks in one chromosome and can be either centric or acentric [31].

Fig.1: Metaphase with one dicentric chromosome and one acentric fragment



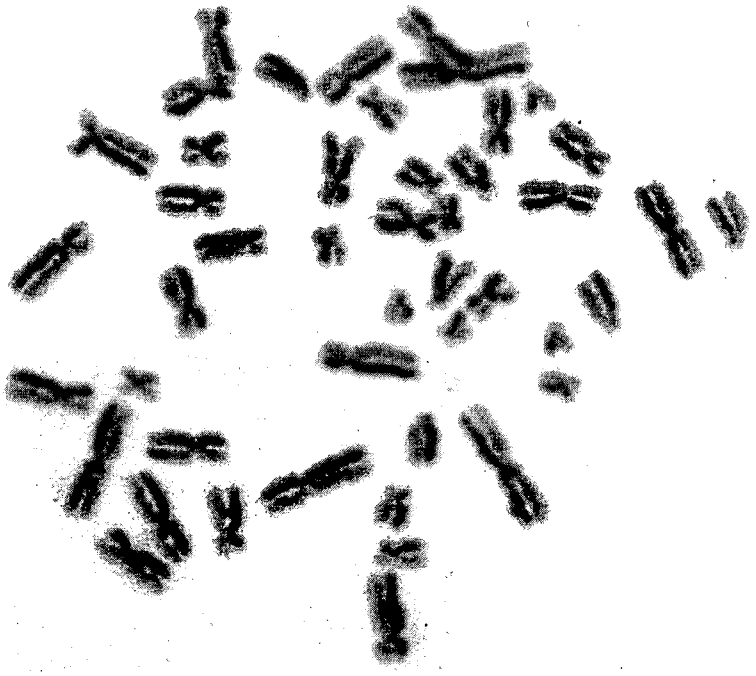
For application in dose assessment the influence of cell proliferation on the aberration frequency has to be considered. Typically the bulk of the stimulated cells may take about 48 hours to complete their first cell-cycle in culture, but nevertheless cells may be in their second mitosis in culture even in samples fixed after 48 hours. Owing to the fact that about 55% of the dicentric chromosomes are lost during the first post-irradiation cell division, chromosome analysis must be carried out by cell-cycling control in only first-division metaphases, identified by fluorescence plus Giemsa staining (Fig. 2, Harlekin pattern) [4,48].

Background frequency

Retrospective dose estimations of low-level exposures are highly dependent on the background frequency of dicentric chromosomes. The variation of the dicentric frequency measured in different laboratories is rather small [7,29,35,66]. From 65 different studies, involving close to 2000 unexposed healthy individuals and more than 211,000 cells, Lloyd et al. determined a mean frequency of dicentrics of 0.55 x 10^{-3} per cell [41]. A summary of six German cytogenetic studies consists of 346 individuals not exposed to ionising radiation except routine medical diagnostic X-rays, analysed 168,285 cells, results in a mean value of 0.49 x 10^{-3} dicentric chromosomes per cell. The frequency of dicentrics in our laboratory control group (25 healthy adult persons, 0.46 x 10^{-3}) is within the range of these investigations of German citizens (Tab. 1).

Bender et al. presented the result of a large human population sample where 353 healthy employees of the Brookhaven National Laboratory were analysed [11]. The mean value of the dicentric background frequency was 1.74 x 10^{-3} per cell, which included 144 individuals classified as „radiation

Fig.2: Second division metaphase, identified by fluorescence plus Giemsa staining (Harlekin pattern)



workers". Also noteworthy is the reported high frequency of dicentric chromosomes in a study of Awa [1] for the Hiroshima control group (2.38 x 10^{-3}). These individuals had probably been exposed to radioactive fallout [60]. Named compilation of control studies shows clearly, that it is extremely important to give careful attention to the selection of control subjects, particularly with respect to potential exposure to ionising radiation.

A multitude of studies have scrutinized the influence on the frequency of dicentrics in control populations on contamination of environmental clastogenic chemicals or medicines. So far, there has been no evidence that factors other than ionising radiation showed a significant influence on the background frequency of dicentric and centric-ring chromosomes in normal unexposed population groups [7,21]. Only a few substances, among them „radiomimetics" are able to induce chromosomal double-strand breaks. The best well-known is the cytostatic drug „Bleomycine". However, in contrast to uniform gamma irradiation „radiomimetics" induce an extreme variation in the number of DNA strand breakages from cell to cell [19,24].

It has to be mentioned that populations with long-term occupationally exposures to clastogenic chemicals, i.e. pentachlorphenol, formaldehyde or mixtures of pesticides, showed a significant increase of the frequency of dicentric chromosomes [3,53]. Moreover these individuals had been exposed to extremely-high concentrations of clastogens. Exposures to environmental pollutants to such an extent can hardly be expected for normal control populations.

Tab.1: Summary of data on frequency of dicentrics in control individuals measured in German cytogenetic laboratories

	Number of samples	Number of cells	Freq. of dic and cr/1000 cells ± SEM
Bauchinger [6]	79	43,000	0.40 ± 0.10
Romm and Stephan [52]	26	16,384	0.85 ± 0.23
Wolf et al. [68]	60	38,600	0.40
Scheid and Weber [56]	16	26,695	0.49
Obe et al. [45]	140	23,831	0.34
Bremen laboratory control	25	19,775	0.46 ± 0.15

By asking every proband to fill in a questionnaire it could be possible to summarize a control population excluding individuals occupationally exposed to clastogenic chemicals.
Conflicting results exist for the influence of age on the frequency of dicentrics in unexposed individuals. Bender et al. observed no significant change in the dicentric frequency with age [12]. Noteworthy here is the fact, that blood samples had been taken from children (with unknown diseases) out of the Departement of Pediatrics of the Medical School of the nearby State University of New York at Stony Brook. However the majority of published studies dealing with a high number of analysed cells pointed out, that the background frequency of dicentrics might be lower in children than in adults (Tab. 2), and additionally there is an increase in aberration frequency with increasing age [39].

Tab. 2: Summary of data on frequency of dicentrics in unexposed newborns and children

	Age group	Number of samples	Number of cells	Freq. of dic and cr/1000 cells ± SEM
Bender et al. [12]	1 - 18 years	44	8,800	1.20 ± 0.40
Ganguly [28]	1 - 10 years	18	1,800	0.56
Padovani et al. [46]	8 - 10 years	10	10,000	0.00
Patil et al. [47]	newborn	522	14,262	0.00
Tonomura et al. [67]	newborn	23	15,325	0.00
Bremen laboratory control	1 - 10 years	10	9,651	0.10

Dose-response relationship

It is a prerequisite for dose estimation that in vivo exposures produce yields of chromosome damage similar to that with in vitro exposure. Actually, it has been proven for whole-body gamma irradiation in various species of animals (rabbit and hamsters) that the frequency of chromosome aberrations in peripheral lymphocytes induced by a given dose, immediately sampled, and cultured after irradiation is essentially the same as that induced in vivo [20,49]. Similar results also exist from whole-body irradiated cancer patients [57], so that dose-effect curves can easily be established for different radiation qualities. Generally, the dose response relationship for high-linear energy transfer (LET) can be described by a linear ($Y = c + \alpha D$), with Y = observed frequency of dicentrics, c = control value) and for low-LET radiations by a linear quadratic dose-response curve ($Y = c + \alpha D + \beta D^2$) [23,27,]. The ratio α/β of the coefficients is equal to the dose at which the linear and quadratic component contribute in equal parts to the formation of dicentric chromosomes. At low doses of low LET-radiations the two chromosome breaks required for dicentric induction are produced by one track of a single ionising particle. At high doses of low LET-radiation the formation of dicentrics also can be due to the track of two or more independent ionising particles, closely interacting in time and space and therefore dependent on the dose and the dose rate [15,62,63].

After homogeneous low-LET irradiation the number of aberrations observed follows a Poisson distribution; after high-LET radiation there will be an excess number of metaphases with multiple chromosome aberrations, the distribution is overdispersed (relative to Poisson) [25].

The detection limit of dose estimation by chromosomal aberration dosimetry depends directly on the number of metaphases analysed. Using a ^{60}Co-gamma calibration curve (0.4 Gy/min, with $\alpha = 0.080 \times 10^{-1}$ Gy^{-1} and $\beta = 4.025 \times 10^{-2} Gy^{-2}$), the lower limit is about 0.17 Gy based on analysing 1,000 metaphases.

The most reliable individual dose assessment can be obtained from acute whole body gamma-exposures. But in radiation accidents non-uniform exposures are the rule and dose estimation is difficult. Inhomogeneous exposures lead to the consequence that the pool of lymphocytes contains cells which can be shown to belong to various categories of exposure. Therefore, after partial-body irradiation, there is an unknown mixture of irradiated and unirradiated populations of lymphocytes. This is why a mean equivalent uniform whole-body dose represents only an approximate approach towards the real dose [40,61].

Decline of dicentric chromosomes

Since dicentric-bearing lymphocytes have a high probability (of 55%) of being lost during mitosis [4], the dicentric frequency declines as the lymphocyte population continuously renews itself after an acute exposure. The later a blood sample is taken from an irradiated person the lower will be the aberration yield in cells observed. Nevertheless, some cells containing unstable aberrations survive many years and can be detected for decades post irradiation [1,38,51]. Several experimental studies performed to quantify this decline have come to divergent conclusions, ranging e.g. from a simple exponential decay with half-lifes of 130 or 160 days in the first year [50,65], or 3 years [17], two exponential decay terms [13,18] with half-lives of about one and five years, a time hyperbolic function and an estimated mean lymphocyte lifetime of ten years [5], a shoulder with an onset of decline not before ten months post exposure [54]. Many of the discrepancies in the reported values are a consequence of diffe-

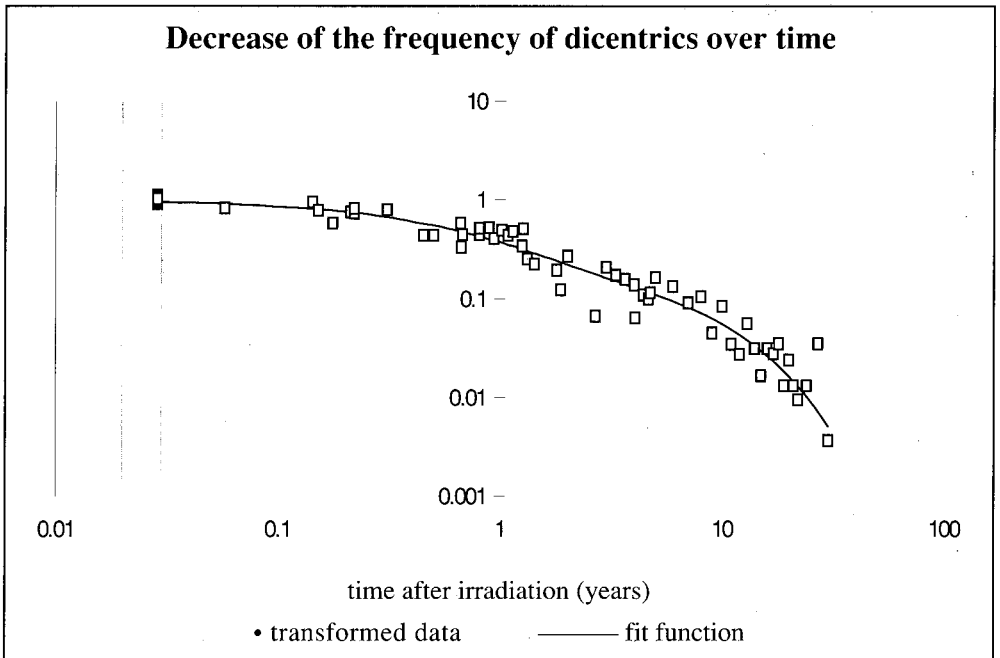


Fig. 3.: Normalized, pooled data on the relative decline of the dicentric frequency from two major studies. The solid line is a fit of Eq.(1) to the data.

rent time intervals, exposure conditions and modelling approaches used.

It was recently demonstrated [37] that under a reasonable set of biological assumptions the general form of the decline curve as a function of dose D and time since exposure t, g(t,D), can be approximated in a mathematical form as set out below:

$$g(t,D) = g_0 [1 + R(D) f(t)] / [1 - S(D) f(t)] \quad (1)$$

Here g_0 is the background dicentric frequency. R(D) is a function describing the dose dependent production of dicentrics by radiation, in units of multiples of background rate, i.e. the dose response curve for the type of irradiation used. S(D) is a similar function describing the dose response of interphase cell killing, an effect leading to dicentric-formation in irradiated lymphocytes. These functions may take different explicit forms depending on radiation quality and exposure conditions. f(t) is a function describing the temporal decline. Under the assumptions chosen it comes out as a sum of exponentials. A key feature of this equation is that the parameter dependencies appear as separable functions of only dose and time, and thus it can be used to pool results of different studies using a common f(t) but different choices for R(D) and S(D) to account for individual exposure conditions. This has been done for the two largest studies published so far [5,18], and the result, normalized to the frequency of dicentrics of one at zero time, is shown in Fig. 3.

The solid line describing the best fit of Eq. (1) to the data yields f(t)=0.54exp(-ln(2)

*t/0.73) + 0.46exp(-ln(2)*t/5.9) with time in years. For low dose applications, the denominator of Eq. (1) is close to unity and f(t) alone gives the relative temporal decline, at higher doses the full Eq. (1) is needed to correct for interphase cell killing.

Applications

Between 1985 and 1989 five cases of leukemia and three other malignancies in children were diagnosed in the community of Sittensen, in northern Germany. For this period the expected value would have been 0.34 cases. A common characteristic of the leukemia cases was multiple X-raying for diagnostic purposes. In order to assess doses phantom studies were performed and chromosome aberration analysis was applied to seven former patients of an orthopaedic practice. Dose assessment for two patients was carried out by using a linear dose effect coefficient given by Hoffmann based on his summary of several authors [33]. The results (see Tab 3) confirm the assumption that the patients were overexposured by diagnostic X-rays [59].

In the region of Ellweiler (Rheinland-Pfalz, Germany), which contains a uranium mine and reprocessing plant, elevated radon levels have been reported. Keller [36] found indoor Radon activities up to 8,000 Bq/m3, 50% of the measurements produced values between 100 and 250 Bq/m^3. Epidemiological analysis of childhood leukemia cases revealed a significant increase of morbility near the facility. Cytogenetic analysis of chromosomal aberrations of 5 juvenile and 5 adults (11,950 metaphases analysed) living in this area yielded an significant increase of dicentric and centric-ring chromosomes (1.67 x 10^{-3} per cell). Dose estimation could not be carried out because of the unknown dose effect relationships after chronic irradiation through incorporated alpha-radionuclides. Nevertheless the elevated frequency of chromosome aberrations strengthened the hypothesis, that ionising radiation was indeed a causal factor for the cluster of childhood leukemia.

Recently in northern Germany a cluster of childhood leukemia cases was reported in the community of Elbmarsch, 25 km southeast of the city of Hamburg [58]. These cases have been linked to the existence of the nuclear boiling water reactor Krümmel, which is located on the river bank opposite the small villages of the community. Krümmel, which began operation is 1984, is the largest boiling water nuclear reactor in Germany (1300 MW_{el}). An extended array of established or suspected risk factors for leukemia has since been investigated by the governments of the two adjacent federal states (Lower Saxony and Schleswig-Holstein) but only background values were

Tab. 3: Physical and biological dosimetry applied to two patients after multiple X-raying

	Number of X-ray treatments	Part of the body	Physically estimated dose	Number of analysed cells	Freq.of dic and cr/ 1000 cells	Biological dose estimation*
1	20	spinal column	19.3 mSv	1,710	6.4	138.5 mGy
2	9	spinal column, pelvis	8.2 mSv	1,042	2.9	58.2 mGy

* Dose estimations were carried out by using a linear dose-effect coefficient (α = [4.36±0.21] x 10^{-5} /mGy) given by Hoffmann [33].

found. The determination of the dicentric frequency by biological dosimetry in 21 adult volunteers in the afflicted region, showed a highly significant elevation with a rate of 1.77 x 10^{-3} per metaphase. This increase in the rate of dicentrics provides evidence that the population of the Elbmarsch community has been exposed to ionising radiation.

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