Journal of Exposure Analysis and Environmental Epidemiology **(1999) 2, 113–133**

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How radiation-specific is the dicentric assay?

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Question: Quantitative cytogenetic analysis of structural chromosome aberrations in human peripheral blood lymphocytes is widely used as an assay to detect and quantify exposure to a variety of clastogens. Unstable chromosome rearrangements, dicentric chromosomes (*dic*) and centric ring chromosomes (*centric r*), are routinely used as biomarkers to assess human exposure to ionizing radiation ("biological dosimetry"). In the moderate- to high-dose range many authors consider the *dic* assay sufficiently radiation-specific for both practical and legal purposes. However, specificity has never been evaluated in quantitative terms. The high sensitivity of the assay would in principle allow for applications in the range of low-dose exposure which has been a major concern in epidemiologic studies. Validity of the assay then critically depends on specificity. **Methods**: A mathematical model is proposed which includes as parameters the decline of dicentric aberrations *in vivo*, the linear dose coefficient for the induction of *dic* and the average total radiation exposure of the population. To assess radiation-specificity of the *dic* assay the equilibrium dicentric rate due to radiation is compared to measurements of the background rate of *dic* in unexposed controls. **Results**: Environmental and medical radiation combined account for at least about 80% of the average background level of dicentrics. **Conclusion**: It is concluded that the dicentric assay is highly specific for ionizing radiation and can therefore be used to assess prior exposure in the dose range of interest in environmental epidemiology.

Introduction

Development and Standardization of the Dicentric (dic) Assay

In 1960, *in vitro* stimulation of peripheral blood cultures made preparations of metaphase chromosomes readily available. Chromosome aberration analysis using human peripheral blood lymphocytes to detect previous exposure to ionizing radiation was among the first applications of the novel technique (Moorhead et al., 1960). In early observational studies radiation-induced unstable chromosome aberrations (dicentric chromosomes *dic*, centric ring chromosomes *centric r*, and acentric fragments *ace*; Standing Committee on Human Cytogenetic Nomenclature, 1985) were detected in lymphocytes of patients during radiation therapy (Tough et al., 1960), after radioiodine therapy, but also after exposure to diagnostic X-rays (Boyd et al., 1961; Stewart and Sanderson, 1961).

Encouraged by the early descriptive studies Bender and Gooch developed a systematic analytical approach (Bender and Gooch, 1962, 1966). To assess exposure doses of eight individuals involved in a radiation accident, they presented cytogenetic results in quantitative terms as rates of *dic* and *centric r* per 1000 metaphases analysed. Individual dose estimates were derived by comparison of these aberration rates to a calibration curve which had previously been established by the authors through irradiation of peripheral blood samples *in vitro*. The now familiar term 'biological dosimetry' originates from Bender and Gooch's account of the peripheral blood lymphocyte as a 'biological dosimeter' (Bender and Gooch, 1962).

Early applications of biological dosimetry included dose assessment after occupational radiation exposure (El-Alfi et al., 1967; Brown and McNeill, 1969; Bauchinger et al., 1971; Popescu and Stefanescu, 1971; Hoegerman et al., 1975), after radiation accidents (Dolphin et al., 1970; Dvoreckij et al., 1971; Brewen et al., 1972; Pjatkin, 1976), in patients undergoing radiotherapy (Tamura et al., 1970; Pyatkin et al., 1972b; Schmid et al., 1974a; Silberstein et al., 1974; Chee and Ilbery, 1975; Watson and Gillies, 1975) or therapy with radionuclides (Arbor, 1964; Cantolino et al., 1966; De la Chapelle et al., 1972; Stevenson et al., 1973; Blackwell et al., 1974; Boyd et al., 1974; Lloyd et al., 1976). Systematic methodological research identified culture time (Buckton and Pike, 1964; Golob et al., 1969; Honda et al., 1969), incubation temperature (Rosenkranz and Veigl, 1980; Purrott et al., 1981), storage conditions of the blood samples prior to the irradiation (White, 1974; Sharma and Das, 1984), gender (Norman et al., 1965; Littlefield et al., 1975; Sharma and Das, 1986), age (Goodman et al., 1969; Liniecki et al., 1971; Patil et al., 1972; Marlhens et al., 1986; Prieur et al., 1988), interdonor-variation (Sharpe, 1969; Sharpe et al., 1969), spatial distribution of the exposure (whole- or partial-body irradiation) (Pyatkin et al., 1972a; McFee, 1977; Liniecki et al., 1983a,b; Poncelet et al., 1988), and decline of induced aberrations *in vivo* (Bender and Gooch, 1963;

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Received 19 September 1997; accepted 7 August 1998.

Norman et al., 1966; Sasaki and Norman, 1967; Schmid and Bauchinger, 1969; Carrano and Heddle, 1973; Braselmann et al., 1986; Das and Sharma, 1987), as major biological sources of variability of the aberration rate.

In vitro dose–response relations were established for calibration purposes for a variety of irradiation conditions such as irradiation temperature (Gumrich et al., 1986), type of radiation (Schmid et al., 1972, 1974b; Todorov, 1975; Bocian et al., 1977; Vulpis et al., 1978; Bauchinger et al., 1983a; Takatsuji et al., 1983; Edwards et al., 1986), dose-rate (Brewen and Luippold, 1971; Purrott and Reeder, 1976; Bauchinger et al., 1979; Lloyd et al., 1984; Fabry, 1986; Guedeney et al., 1988), energy spectra (Neary et al., 1967; Neary et al., 1972; Virsik et al., 1980; Schmid et al., 1984; Fabry et al., 1985), and linear energy transfer (LET), respectively (Scott et al., 1969, 1970; Lloyd et al., 1975; Virsik et al., 1977; Dolphin, 1978). It became evident, that in order to maximize sensitivity as well as precision the method required major standardization efforts. Several multilaboratory endeavours established standardized culture, mounting, and scoring protocols (Bianchi et al., 1982; Pohl-Rüling et al., 1983, 1986; Lloyd et al., 1992). First results indicated that in order to prevent induced aberrations from being altered ("derived chromosome aberrations") or lost in subsequent mitoses, aberration analysis must be restricted to first metaphases in culture (M1) (Crossen and Morgan, 1977; Scott and Lyons, 1979). Control of M1 is usually achieved by application of the 'fluorescence plus Giemsa' differential staining (FPG) (Perry and Wolff, 1974). The resulting gain in sensitivity was confirmed experimentally (Wagner et al., 1983).

Biological dosimetry today is routinely applied to a variety of exposures from various sources and in different dose ranges, though predominantly in the range of low doses. The assay has also been adopted by radiation protection authorities of various countries in order to quantify the significance of exposures in cases of alleged or actual radiation accidents (Stephan, 1987; Lloyd et al., 1988b; Wolf et al., 1991).

Further to *dic* being the single most extensively validated biomarker for radiation exposure, structural chromosome aberrations are presently the only marker with an established predictive value for increased cancer risk (Hagmar et al., 1994; Bonassi et al., 1995). Hence, according to a scheme by Hulka and colleagues *dic* can both serve as markers for biologically effective dose and markers for early response in epidemiological studies (Hulka, 1990; Schwartz, 1990).

Sensitivity

Authors generally agree on the high sensitivity of the method even in the very low dose range. Significant elevations of *dic* and *centric r* were observed in populations exposed to environmental radiation. Various sources of exposure were considered, among these elevated levels of terrestric background radiation (Barcinski et al., 1975; Pohl-Rüling and Fischer, 1983; Wang et al., 1990), cosmic radiation (Scheid et al., 1993; Heimers et al., 1995), atmospheric (Pohl-Rüling and Fischer, 1979) and waterborne radon (Stenstrand et al., 1979), workers with occupational radiation exposures within permissible dose-limits (El-Alfi et al., 1967; Bauchinger et al., 1971, 1980; Popescu and Stefanescu, 1971; Brandom et al., 1978a,b; Evans et al., 1979; Lloyd et al., 1980, 1988b; Scheid and Traut, 1983, Scheid et al., 1990; Romm and Stephan, 1990; Gensicke et al., 1991), after exposure to diagnostic levels of medical irradiation (Bloom and Tjio, 1964; Kumagai et al., 1990; Jha and Sharma, 1991; Barquinero et al., 1993; Schmitz-Feuerhake et al., 1994; Weber et al., 1995), and in individuals exposed to radioactive fallout after the Chernobyl nuclear accident (Stephan and Oestreicher, 1989; Arndt et al., 1991; Pohl-Rüling et al., 1991). The high sensitivity of the assay would in principle accommodate application to the very low-dose range. Its validity therefore critically depends on its specificity, i.e., the extent to which even small elevations of the *dic/centric r* rate do in fact establish a prior exposure to radiation rather than to any other occupational or environmental clastogen.

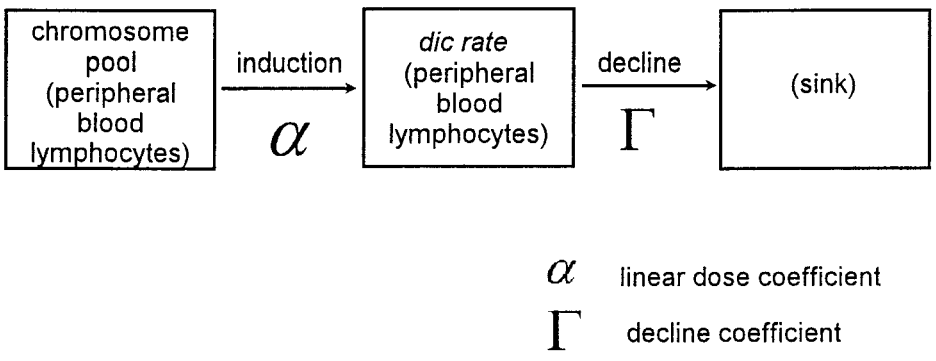

Figure 1. Three-compartment model of the *dic* background rate.

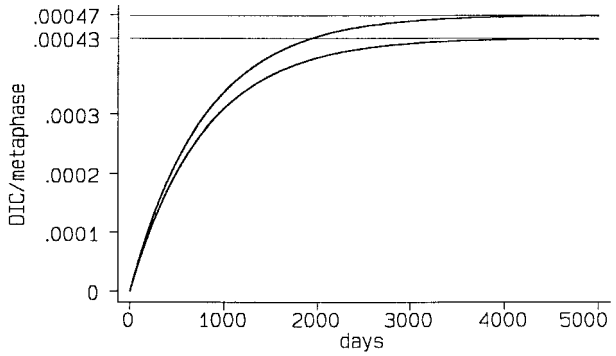

Figure 2. Model-based prediction of the background *dic*-rate. Upper curve: 25% lymphoid tissue dose due to radon; lower curve: 18.7%; derivation of parameter estimates below.

Specificity

Specificity, on the other hand, has rarely been addressed explicitly in the literature on biological dosimetry. In major reviews specificity for ionizing radiation is unequivocally considered a matter of fact. However, radiation specificity is either only briefly mentioned (Stephan, 1987; Bender et al., 1988a; Hoffmann et al., 1991; Müller and Streffer, 1991) or rather tacitly assumed (Dolphin and Purrott, 1971; Abbatt et al., 1974; Bianchi et al., 1982; Stephan, 1983; Weber, 1990).

The high sensitivity for ionizing radiation together with the low background rate for both *dic* and *centric r* in unexposed control populations (Lloyd et al., 1980; Bauchinger et al., 1983b; Richardson et al., 1984; Stephan, 1987; Wolf et al., 1991; Heimers et al., 1995) provides some indirect clue toward the specificity of the assay.

A theoretical approach derives specificity of the *dic* assay for ionizing radiation from the biokinetic mechanism of the induction of rearrangement aberrations. It is today generally agreed upon that the formation of *dic* ultimately requires the induction of two molecular changes in the DNA ("sublesions") (Lea and Catcheside, 1942; Lea, 1956). Experimental evidence has established DNA double-strand breaks (DSB) as the major biological substrate of the theoretically postulated 'sublesion' (Bender et al., 1974; Virsik-Peuckert, 1981; Holmberg and Gumauskas, 1986; Natarajan et al., 1986; Goodhead and Nikjoo, 1989; Holmberg, 1990; Natarajan, 1993).

In order for interaction to take place these DSB must occur simultaneously in both space and time. The majority

Table 1. Sources of radiation exposure to lymphoid tissue of unexposed controls (published figures for derived effective dose equivalents are assumed to represent lymphocyte doses[a]).

Source	Annual lymphocyte dose[a] (mSv/year)			Reference
	External	Internal	Total	
1. Natural radiation				UNSCEAR, 1988; Hölzer, 1993
Cosmic rays				
Gamma component	0.30	–	0.30	
Neutron component[b]	0.14	–	0.14	
Cosmogenic radionuclides (incl. K-40, Rb-87)	0.15	0.20	0.35	
U-238, Th-232 series[b] (excl. radon inhalation)	0.26	0.66	0.92	
Radon inhalation (18.7% contribution)[c]	–	0.75	0.75	
Radon inhalation (25% contribution)[c]	–	1.00	1.00	
2. Man-made radiation				
(a) Diagnostic medical radiation	1.50	–	1.50	Bauer et al., 1993; Burkhardt and Tillmanns, 1993; Veit et al., 1993
(b) Technical/industrial radiation, atomic power plants	0.02	–	0.02	Burkhardt and Tillmanns, 1993
(c) Fallout from nuclear weapons testing	0.01	–	0.01	UNSCEAR, 1988
Annual total				
Estimate I[c]	2.38	1.61	3.99	(mSv/year)
Estimate II[c]		1.86	4.24	
Daily total				
Estimate I[c]			0.011	(mSv/day)
Estimate II[c]			0.012	

[a]The doses to the PHA-sensitive lymphocyte fraction, since in routine biological dosimetry almost only these are forming metaphases. Hence observed *dic* rates refer almost exclusively to this compartment of the lymphoid tissue.
[b]With a quality factor $Q = 25$ for densely ionizing components (according to Kuni, 1994).
[c]Calculated for a mean indoor radon concentration of 49 Bq/m^3 (Urban et al., 1985), derived organ dose for PHA-sensitive lymphocyte fraction. The two estimates refer to the proportion of the total dose which is attributable to radon-222 (Estimate I: 18.7%; Estimate II: 25%; see Figure 2 and discussion).

Table 2. Dose–response data from *in vitro* irradiation experiments of full blood samples.

A. X-rays of different spectra						
Type of radiation, radiation conditions	Dose-rate (mGy/min)	Dose range (mGy)	Experimental conditions	Cytogenetic endpoint(s)	Metaphases per dose	Reference
180 keV X-rays (18 mA, 1 mm Cu-filter, room temperature)	115	0-575	3 healthy donors 50 h cultures (incl. 3 h Colcemide)	*dic* + *centric r*, (only with accompanying *ace*), *ace*	1500–3200	Ziemba-Zoltowska et al., 1980
220 keV X-rays (14 mA, 3.35 mm Cu filter, 37°C)	160	0–500	1 healthy donor 48 h cultures (incl. 3 h Colcemide) FPG	*dic*, excess *ace*	2000–3000 (control: 24,000)	Wagner et al., 1983
200 keV X-rays (2–15 mA, 1.0 mm Cu filter, room temperature)	23–170	0–300	2 donors 48 h cultures (incl. 3 h Colcemide) FPG coordinated experiment with 10 participating laboratories	*dic*, *centric r*, terminal *del*, interstitial *del*	4300–9900	Pohl-Rüling et al., 1983
30–150 keV X-ray (220 kVp) (12.5–14 mA; 37°C)			2 donors 48 h cultures (incl. 3 h Colcemide) FPG	*dic*, excess *ace*	500–3000	Schmid et al., 1984
(a) 2.0 mm Al + 3.35 mm Cu (HVL 2.76 mm Cu)	(a) 160	50–4000				
(b) 4.05 mm Al + 0.5 mm Cu (HVL 1.32 mm Cu)	(b) 500	50–4000				
169 keV X-rays (HVL = 4.3 mm Cu; 37°C)	3–43	0–300	4 healthy donors 48 h cultures (incl. 3 h Colcemide) FPG in sample slides coordinated experiment with 6 participating laboratories	*dic*, *centric r*, excess *ace*	11,500–12,000	Lloyd et al., 1988a, 1992

169 keV X-rays (HVL = 4.3 mm Cu; 37°C)	3–43	0–300	20 healthy donors 48 h cultures (incl. 3 h Colcemide) FPG in sample slides coordinated experiment with 6 participating laboratories	*dic*, *centric r*, excess *ace*	4000–10,000	Lloyd et al., 1992
B. Co-60 gamma rays						
Co-60 (37°C)	(a) 17 (b) 500	0–4000	1 healthy donor, 448 h cultures (incl. 3 h Colcemide) FPG	*dic*, excess *ace*	600–3000	Bauchinger et al., 1983b
Co-60 (37°C)	100	100–2000	1 healthy donor 48 h cultures (incl. 3 h Colcemide)	*dic*	200–600	Stephan, 1983; Stephan et al., 1983
Co-60 (37°C)	0.39–89.5	100–5500	48 h cultures (incl. 3 h Colcemide) FPG	*dic*, *centric r*, excess *ace*	500–9000	Lloyd et al., 1984
(a) Co-60 (room temperature) (b) 250 keV X-rays (15 mA, 0.5 mm Cu filter, room temperature)	(a) (some 200) (b) 1000	0–2000	2 healthy donors 45–46 h cultures (incl. 3 h Colcemide) M1/M2-ratio controlled in preliminary experiment (M2 < 4.5%)	*dic*, *centric r*, *ace*	200–2000 (control: 6000)	Fabry et al., 1985
Co-60 (37°C)	(a) 0.5 (b) 1.7 (c) 400	(a), (b) 100–2000 (c) 50–2000	(a), (b) 1; (c) 2 healthy donors (a), (b) 44–45; (c) 46 h cultures (incl. 3 h Colcemide) M1/M2-ratio controlled in preliminary experiment (M2 < 4.5%)	*dic*, *centric r*, *ace*	200–2000	Fabry, 1986

of rearrangements takes place within minutes after the DSB have been induced, and the maximum interaction time is only about 2 h (Purrott and Reeder, 1976; Schmid et al., 1976; Lloyd et al., 1984). The interaction distance is in the range of 10–100 nm (Virsik and Harder, 1980, Virsik et al., 1980), with a higher probability towards smaller distances (Holmberg, 1990).

This has implications for specificity: Ionizing radiation produces DSB in close temporal and spatial proximity—along 'tracks' while traversing the nucleus and, hence, maximizing its effectiveness in the induction of *dic*.

The great majority of chemical mutagens, on the other hand, are incapable of inducing DSB in the first place. Only few chemicals, referred to as 'radiomimetic' (e.g., Streptonigrin, 8-Ethoxycaffeine, Bleomycin, *m*-AMSA) can induce DSB. They do so, however, in a much more random fashion with respect to space and time, thus limiting the probability for any interaction between the resulting DSB. Rather than interacting in the formation of *dic*, chemically induced DSB therefore are more likely to give rise to acentric fragments (*ace*). As an important theoretical consequence, a higher ratio of *dic/ace* for ionizing radiation as compared to a chemical exposure would be expected, which is indeed supported by experimental data (Coppola et al., 1986; Vulpis and Coppola, 1990).

The absence of accompanying *ace*, on the other hand, could indicate that a *dic* is 'derived' from an initial chromatid-type aberration such as a triradial or quadriradial. Such *dic*, however, are extremely rare in first metaphases in culture rendering this potential mechanism negligible in quantitative terms (Tucker and Preston, 1996; Bauchinger, 1995). Consequently, in order to interpret an increased rate of *dic* in terms of an induction through ionizing radiation, the rate of lost as well as excess ('unbalanced') *ace* needs to be considered.

The significance of these distinctions increases toward the low dose range. While the probability of induction of two DSB in sufficient proximity through a radiomimetic chemical decreases rapidly for lower doses, any dose of ionizing radiation, even a single track, can in principle induce a *dic*. The probability of single track *dic* increases with increasing LET in a systematic fashion (Scott et al., 1969, 1970; Lloyd et al., 1975; Virsik et al., 1977; Dolphin, 1978).

Moreover, radiomimetic chemicals are well-known human clastogens and strictly regulated, rendering significant and inadvertent exposure of the general population to these chemicals highly unlikely.

Sources of the Background Aberration Rate

The background level of rearrangement aberrations in peripheral lymphocytes of unexposed controls is generally referred to as 'spontaneous'. This is a common misconception, since any *dic/centric r* must have been induced by some clastogenic action in the first place. Sources of this initial action are supposed to be predominantly exogenous, although in principle there could be endogenous sources, too. Hence the background *dic* and *centric r* rate in a population represents the net cytogenetic response to all clastogenic exposures in that population. The mere finding that background levels for *dic* are always low proves that none of the exposures that are prevalent in the general population appears capable to induce substantive amounts of rearrangement aberrations. In other words, the variety of potential and actual environmental exposures has at most a small impact toward the induction of *dic* and *centric r*, if any.

However, whereas this qualitative approach might suffice for most practical purposes, it is scientifically unsatisfactory and obviously does not readily extend to the very low dose range. Recent findings of elevated *dic* rates in adults living close to a nuclear reactor in northern Germany have generated considerable debate about whether or not exposures other than ionizing radiation may have given rise to dicentric chromosomes in this population *in vivo* and, if so, to what extent (Schmitz-Feuerhake et al., 1993, 1996). In order to reasonably interpret these findings it becomes crucial to discuss specificity in quantitative terms using an experimental approach.

Methods

The lack of experimental data on many of the numerous established or suspected human clastogens in the occupational sphere and the general environment so far precludes a complete direct assessment of their potential to induce unstable rearrangements. Moreover, there is still only rudimentary information on the synergistic effects of complex mixtures of clastogens to which parts of the general population could be exposed.

To circumvent the limitations in this paper we therefore use an indirect approach. In a simple three-compartment catenary model of the background rate of *dic* the relative contribution of the main components of radiation exposure in the general population (natural background radiation, medical radiation exposure) will be calculated. Perfect specificity would require the background level to be exclusively attributable to radiation exposure from these sources, i.e., no other clastogen must contribute to the background rate of *dic*. Hence, the proportion of the spontaneous *dic* rate that can be explained in terms of radiation exposure can be used as a quantitative measure for specificity.

Modelling the dic Rate in Unexposed Controls

Model Assumptions

1. Background rates of *dic* and *centric r* in peripheral blood lymphocytes in adults as measured by us and in

various other laboratories represent an equilibrium between newly induced aberrations and the decline of existing aberrations.

2. The average total exposure to ionizing radiation from natural and man-made sources is constant over time.

3. Published data on background rates represent the general adult population in Europe and the USA.

4. The decline with time of the rate of *dic* in peripheral blood lymphocytes can be reasonably approximated with a simple exponential equation (i.e., the half-life of *dic* is constant with time).

5. The linear dose coefficient obtained from *in vitro* irradiation of blood samples with low-LET radiation in the low-dose range can be used to approximate the net linear dose coefficient *in vivo* for induction of *dic* through natural background radiation and medical-diagnostic radiation, respectively.

The molecular mechanism of induction of *dic* and *centric r* is very similiar, but the latter are much less frequently observed (about 1 *centric r* for each 10 *dic*). Since the decline kinetic of *dic* and *centric r* is distinctly different, we restrict the model to *dic*.

The background rates of *dic* can then be regarded as the result of two competing processes: (1) Induction through the net effect sum of all clastogens, characterized by a linear dose coefficient α and (2) the decline of *dic* carrying peripheral lymphocytes, described by a transfer rate constant (Figure 1).

The rate of change of the *dic*-rate in peripheral blood lymphocytes with time t can then be described by a first-order differential equation (Eq. (1)):

$$\frac{\mathrm{d}y}{\mathrm{d}t} = \alpha \cdot \overline{D} - \Gamma \cdot y(t) \qquad (1)$$

where $\overline{D}$ = average dose rate (mSv/year), α = linear coefficient (1/mSv), Γ = decline coefficient (1/year), $y(t)$ = *dic*-rate at time t.

Eq. (1) can be solved in closed form. Assuming no *dic* at $t = 0$ (say, at the time of the organogenesis of the lymphatic system in fetal life), the *dic*-rate at any time t can be expressed solely in terms of the model parameters (Eq. (2)):

$$y(t) = \frac{\alpha \cdot \overline{D}}{\Gamma}\left(1 - \mathrm{e}^{-\Gamma t}\right) \qquad (2)$$

With the parameter estimates derived in this paper, a saturation rate of 0.00043 *dic* per metaphase is reached after some 10 to 11 years of age (about 4000 days). The predicted background rate remains constant for older ages (Figure 2).

For infinite t, the *dic*-rate approaches a saturation rate which is denoted y_s (Eq. (3)):

$$\lim_{t \to \infty} y(t) = \frac{\alpha \cdot \overline{D}}{\Gamma} = y_s \qquad (3)$$

Being a transfer rate constant, Γ can be expressed in terms of the half-life of *dic* in peripheral blood lymphocytes (Eq. (4)):

$$\boldsymbol{t}_{1/2} = \frac{\ln 2}{\Gamma} \qquad (4)$$

with $\boldsymbol{t}_{1/2}$ = half-life of *dic* in peripheral blood lymphocytes

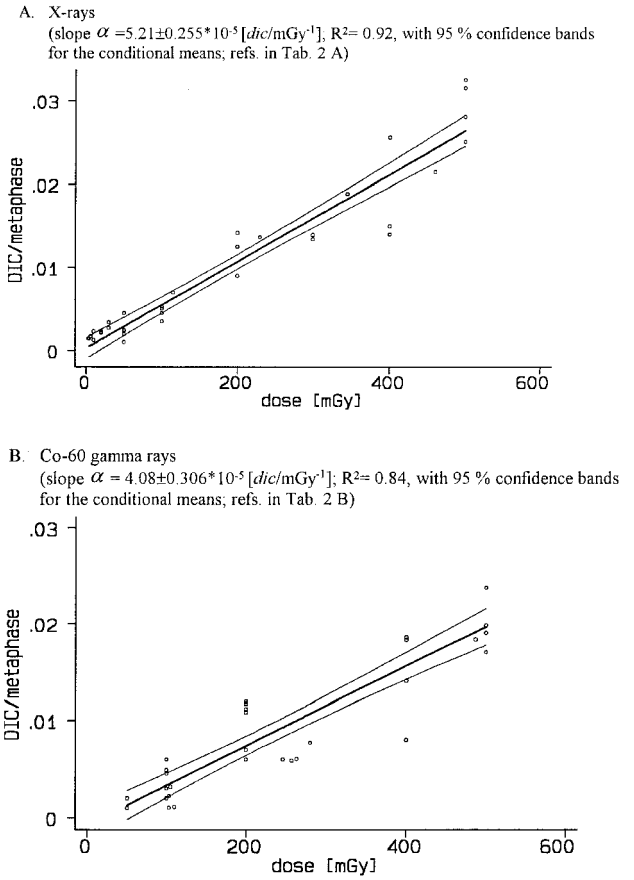

Figure 3. Dose–response for *dic* in human peripheral lymphocytes (0–500 mGy). (A) X-rays (slope $\alpha = 5.21 \pm 0.255 \times 10^{-5}$ [*dic*/mGy^{-1}]; $R^2 = 0.92$, with 95% confidence bands for the conditional means; refs. in Table 2A). (B) Co-60 gamma rays (slope $\alpha = 4.08 \pm 0.306 \times 10^{-5}$ [*dic*/mGy^{-1}]; $R^2 = 0.84$, with 95% confidence bands for the conditional means; refs. in Table 2B).

Hence, the model for the background rate of *dic* in peripheral blood of unexposed controls is defined by three parameters:

1. the net dose rate $\overline{D}$ of radiation exposure in 'unexposed' controls
2. the linear dose coefficient α for the induction of dicentric chromosomes through ionizing radiation
3. the decline constant Γ representing the net effect of all processes which are capable of reducing the *dic* rate in peripheral blood lymphocytes over time.

Natural Background Radiation and Radiation from Artificial Sources $\overline{D}$

The average radiation exposure of an adult typically consists of three main components: Natural background radiation, exposure to the natural noble gas Radon-222 and its decay products (which is of natural origin, however becomes relevant because of civilisation conditions i.e., living in houses) and exposure out of artificial sources, mostly medical radiology and predominantly applied for diagnostic purposes.

Table 1 shows estimated figures for the general population of Germany.

The Linear Dose Coefficient α

The linear coefficient characterizes the dose–response relation for *dic/centric r* induction by sparsely ionizing radiation in the low to moderate dose range. The value of α can be derived from experiments where samples of human peripheral blood were irradiated *in vitro*. To be eligible for this analysis, experiments must have applied a standardized culture protocol including M1 control, culture time, and preparation procedures. In order to represent the range of LET of sources of radiation exposure for 'unexposed' controls in terms of LET, only experiments using cobalt-60 gamma rays or X-rays of 150 keV or higher were selected (Table 2).

Figure 3 shows a meta-analysis of recent experimental data in the dose range 0–0.5 Gy. The data were fitted by a linear regression model. Separate linear regression analyses were performed for data points obtained by irradiation with Co-60 gamma rays ($\alpha = 4.08 \pm 0.306 \times 10^{-5}$ [dic/mGy^{-1}]; $R^2 = 0.84$) and X-rays ($\alpha = 5.21 \pm 0.255 \times 10^{-5}$ [dic/mGy^{-1}]; $R^2 = 0.92$), respectively. Ninety-five percent confidence intervals were calculated for the slopes and the conditional means.

Decline Γ

Table 3 summarizes published data on the decline of *dic* rates in peripheral lymphocytes *in vivo*. The majority of the studies presented so far have followed patients after radiation therapy. Exceptions are the studies by Brewen et al. (1972), Dolphin et al. (1973), Scheid et al. (1988), and

Table 3. Decline of *dic* rates in peripheral lymphocytes after acute irradiation (exponential regression of original data).

Individuals, exposure conditions, dose range	Number of individuals	Total follow–up (years)	Decline $\Gamma(\pm\mathrm{SE})$ in 1st 2000 days (10^{-3}/day)	Half-life $t_{1/2}$ (*dic*) (days)	Reference
Female patients, radiation therapy with external gamma irradiation and radium implants of the lower pelvic region for cervical carcinoma (total tumor dose 60–80 Gy)	36	4–13	1.777(±0.216)	396(±49)	Norman et al., 1966
Female patients, radiation therapy with external gamma irradiation (tumor dose 34–39.5 Gy) and radium implants (4000–5000 mgeh) of the lower pelvic region for gynecological carcinomas	84	6	1.310(±0.122)	534(±50)	Schmid and Bauchinger, 1969
Worker, accidental exposure to Co-60 gamma radiation, total body dose about 2 Gy	1	0.4	5.90(±0.11)	117(±23)	Brewen et al., 1972
Worker, accidental exposure with consecutive erythema of the chest (estimated skin dose > 50 Gy in a small area of 7-cm diameter)	1	2.4	0.941(±0.255)	799(±210)	Dolphin et al., 1973
Patients, radiation therapy of sacroiliac joints and lumbal spine for ancylosing spondylitis (Bechterew) (250 kV X-rays, applied in 10 fractions, total dose 15 Gy)	200	20	1.186(±0.171)	597(±86)	Buckton et al., 1978
Worker, accidental exposure in industrial radiography (X-rays, estimated partial body doses: chest 6 Sv, right hand 12 Sv)	1	4	1.340(±0.418)	573(±179)	Scheid et al., 1988
Male patients, radiation therapy of inguinal and paraaortic fields for seminoma (61,9-225 J)	23	4.7	1.378(±0.110)	507(±41)	Bauchinger et al., 1989
Individuals from the general population, accidentally exposed in the course of a radiation incident in Goiania, Brazil (inhomogenous external and internal exposure to Cesium-137 gamma radiation. Estimated individual equivalent whole body doses in the range of 1–4 Gy	10	1	5.261(±0.883)	136(±23)	Ramalho and Nascimento, 1991

Ramalho and Nascimento (1991), who followed patients after accidental irradiation. Scheid et al. monitored an industrial radiographer for about 4 years after he had been involved in a radiation accident related to his occupation (Scheid et al., 1988). Dolphin et al. reported briefly on a worker, who had been accidentally exposed in at least two independent events and suffered severe partial body doses to a small area on his chest. Follow-up time was about 29 months (Dolphin et al., 1973). Brewen et al. compared physical and biological dosimetry after accidental whole-body Co-60 gamma radiation exposure of an employee in a University laboratory. *Dic* rates were recorded for 137 days post accident. Ramalho and Nascimento studied a cohort of people who had been involved in the radiation accident in Goiania, Brazil (Ramalho and Nascimento, 1991).

Numerical values for Γ and $t_{1/2}$ were obtained by fitting an exponential regression model (i.e., a linear regression model of the log *dic* rate) to each of the original datasets separately. To facilitate comparisons between the

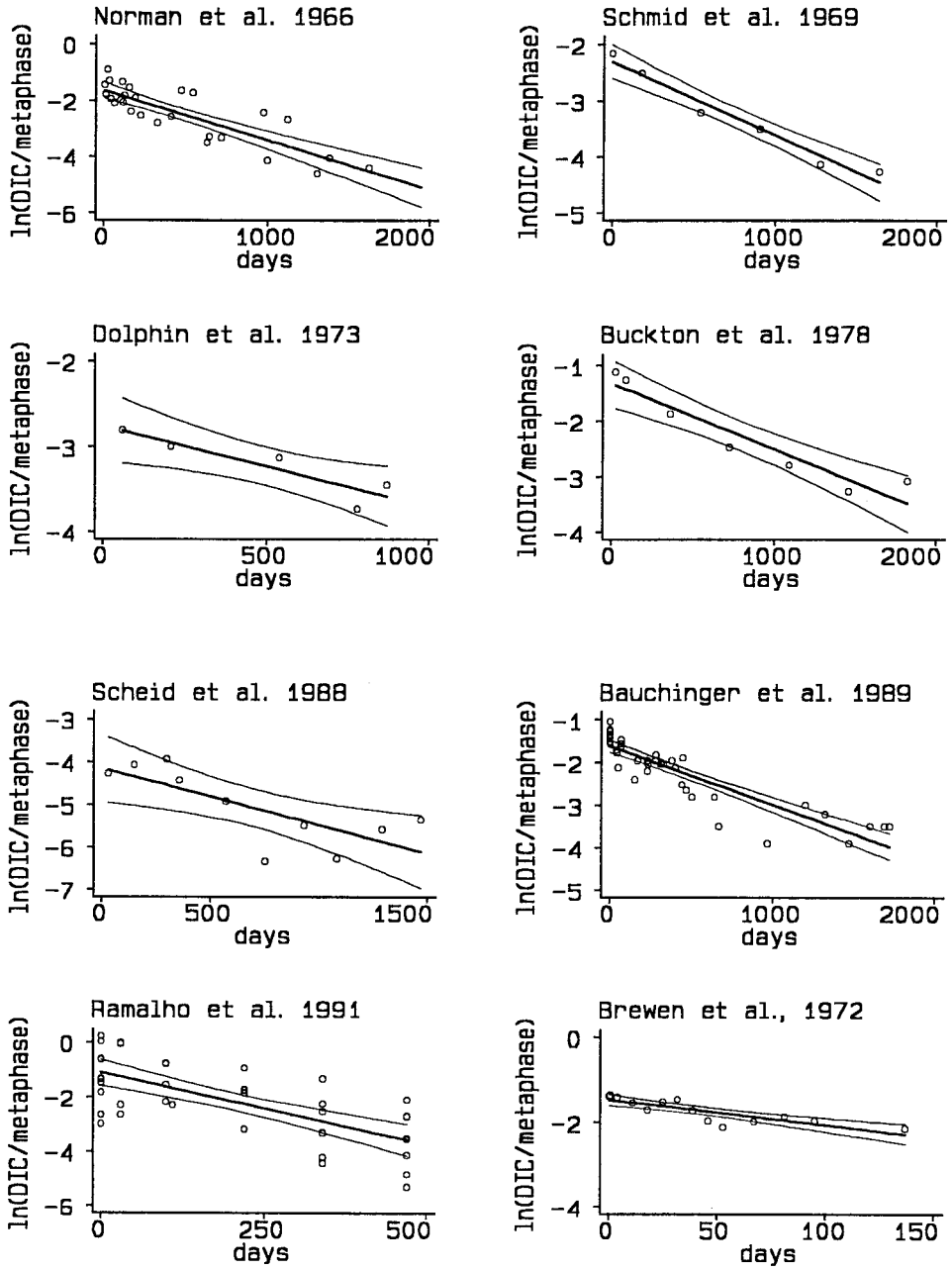

Figure 4. Published data on the decline of the *dic* rate in peripheral blood lymphocytes (linear regression after log-transformation of the *dic* rate, 95% confidence bands for the conditional means; refs. in Table 3).

respective coefficients follow-up times were censored at 2000 days. Figure 4 shows the respective fits to each individual data set used for the derivation of Γ.

Discussion

Discussion of Model Parameters

Dic versus Centric r

Structural chromosome aberrations have been observed in many occupational settings and have been ascribed to a variety of chemical exposures. In many instances, however, authors do not specify the particular types of aberrations they have observed or report only pooled results for *dic*, *centric r*, and *ace*. However, radiation specificity evidently cannot be assumed for all classes of structural chromosome aberrations. In this paper we discuss chromosome rearrangements exclusively. We have moreover focused on unstable *dic* and *centric r* rather than stable translocations since detection of the latter requires considerable modification of the assay. Given the similarity of the molecular mechanism and the kinetics of the induction it is conceivable that the considerations toward radiation specifity presented herein could readily extend to stable chromosome rearrangements.

The average level of *dic* in peripheral blood lymphocytes in unexposed individuals ('spontaneous' *dic* level) is defined herein as a dynamic equilibrium of induction and decline of rearrangements. As we have pointed out above, the measurable equilibrium rate of *dic/centric r* is explained in terms of the factors $\overline{D}$, α, and Γ, respectively. Numerical values for these parameters have been obtained from various literature sources. The degree of precision is discussed below, together with some limitations of the data.

Linear Dose Coefficient α

In vivo, new *dic* are continuously induced through radiation exposure. The dose–response relationship has been investigated by means of a meta-analysis of published data obtained from *in vitro* irradiation experiments with human peripheral blood lymphocytes.

Second-degree polynomials (i.e., linear–quadratic dose–response curves) were fitted to the experimental data by the least-squares method. For both Co-60 gamma and X-ray radiation the quadratic coefficients were 2–3 orders of magnitude lower than the linear coefficients and were not statistically significant from zero. Hence the dose–response relation appeared linear in the dose range studied (0–500 mGy; Co-60 gamma rays: $R^2 = 0.84$; X-rays: $R^2 = 0.92$) which is typical for sparsely ionizing radiation. The dose–response relation for the induction of *dic* can thus be represented by a linear dose coefficient α. The slope was somewhat steeper for X-rays ($\alpha = 5.21 \pm 0.255 \times 10^{-5}$ [*dic*/mGy]) than for Co-60 gamma rays ($\alpha = 4.08 \pm 0.306 \times 10^{-5}$ [*dic*/mGy]). This finding is expected and generally believed to reflect the different LET of the two kinds of radiation. For non-corpuscular radiation the LET decreases with increasing photon energy by a factor of three (ICRU, 1986). Hence, X-rays are generally more efficient in inducing *dic* than are Co-60 gamma rays (Neary et al., 1967; Scott et al., 1970; Lloyd et al., 1975; Virsik et al., 1977; Schmid et al., 1984).

Although we believe the α values derived here to be generally representative for *in vivo dic* induction in the low-dose range it must be noted that a substantial proportion of the overall radiation exposure of unexposed controls actually involves radiation of higher LET (most medical procedures, radon, fast neutrons, other corpuscular radiation). Excluding these in the derivation of numerical values for α is conservative with respect to the question at hand since it tends to underestimate the real 'net'—slope of the dose–response relation between dose and the *dic* rate for the combined *in vivo* exposures of the general population and, hence, the proportion of the background *dic* rate attributable to it.

For our purposes we have calculated a weighted average of the slopes for Co-60 gamma rays and X-rays. The weights are constructed by dividing the total average radiation exposure (Table 1) of the population into 'high' and 'lower' energies. Cosmic gamma rays, cosmogenic radionuclides, technical/industrial radiation, and fallout from nuclear weapons testing contribute to the weight assigned to the slope obtained for Co-60 gamma radiation ('high' energy). Radiation from all remaining sources is assumed to be of 'lower' energy.

Hence the numerical value for α becomes:

$$(4.08 \times 10^{-5} * 0.68 + 5.21 \times 10^{-5} * 3.42)/4.10$$

$$= 5.02 \times 10^{-5}\left[\, dic/(\text{metaphase} * \text{mSv})^{-1}\right]$$

If standard errors of the two estimates are treated similarly, the resulting standard error for the combined estimate becomes 0.263.

Decline Γ

Monitoring the decline of *dic* and C-ring rates *in vivo* requires repeated measurements of individuals over several consecutive years. In order to allow for reasonably stable estimates of the decline, individuals must have had considerable *dic* rates in the first place, requiring exposures in the medium- or high-dose range. Few researchers have undertaken such an effort.

The majority of published data were obtained from patients after radiotherapy for benign or malignant disease. Though irradiation conditions, geometry, and total doses varied considerably between the cohorts, log–linear regression of the original data from four different studies yielded similar decline constants between $1.186(\pm 0.171)$ and $1.777(\pm 0.216)$ (Norman et al., 1966; Schmid and Bauchinger, 1969; Buckton et al., 1978; Bauchinger et al., 1989). These values correspond to half-lives of *dic* in peripheral lymphocytes ranging approximately between 400 and 600 days (Table 3).

Observations obtained for individuals after accidental radiation exposure are generally in line with the findings in the patient cohorts (Dolphin et al., 1973; Scheid et al., 1988). Smaller numbers of metaphases analysed explain the somewhat greater variability (half-life 573 to 799 days).

The findings of both Ramalho and Nascimento and Brewen et al. represent noteworthy exceptions, in that they yield a much shorter half-life for *dic* in peripheral blood lymphocytes of 10 individuals accidentally exposed to cesium-137 (Ramalho and Nascimento, 1991) and on a university employee after accidental whole-body gamma-irradiation of about 2 Gy (Brewen et al., 1972). Ramalho and Nascimento included individuals who had presented with clinical signs of radiation sickness (marked depletion of lymphocytes). Similar hematological consequences must be assumed for the patient followed by Brewen and colleagues. In both cases, the much faster decline could be partially attributable to a 'dilution' of *dic*-carrying lymphocytes in the blood through normal lymphocytes during increased regeneration rather than to a 'real' degradation of *dic*-carrying lymphocytes.

Guedeney et al. (1988) also provide supporting evidence. The authors repeatedly measured *dic* rates of three individuals who had been accidentally exposed to cobalt-60 and iridium-192 gamma radiation. Initial biological dosimetry had revealed equivalent whole body doses of 1–1.4 Gy. Half-lives of *dic* derived over a period of 210 days after exposure were only about 120 days. A decline constant, however, could not be calculated since authors do not provide their original data.

As follow-up of both Ramalho and Nascimento's cohort and the university employee (Brewen et al., 1972) is short the magnitude of a 'dilution' effect is likely to be considerable, however cannot presently be assessed in quantitative terms. Hence decline constants derived from these data are hardly representative for the unexposed general population and are therefore excluded from the meta-analysis presented herein.

To prepare for a combined estimate of Γ the data were standardized to an intercept of zero. To do this, the intercepts were estimated by log–linear regression analysis for each dataset separately and the respective estimates were then subtracted from the *dic*-rate for each data point. After standardization the data from all six studies were pooled and a weighted log–linear regression with no intercept in the model was performed (weights = number of metaphases analysed for each data point). This analysis yields a combined estimate of $\Gamma = 1.285 \times 10^{-3}$ (1/day) with a standard error of 0.0515×10^{-3} (F-value 621, $R^2 = 0.87$; $p < 0.0001$) corresponding to a half-life of about 540 days (Figure 5).

Figures 4 and 5 demonstrate that straight lines in log–linear plots fit the original data reasonably well. However, on close inspection, it appears that half-lives of *dic* in peripheral blood lymphocytes could increase with time rather than being constant. This has been found rather consistently for long follow-up periods. Buckton et al. originally fitted two separate regression lines to their data (0–4 years, 4–20 years), the first of which had a distinctly steeper slope than the latter (Buckton et al., 1978). More recently Bauchinger et al. obtained the best fit applying a time–hyperbolic model rather than a simple exponential model (Bauchinger et al., 1989). Guedeney et al., as well as Doloy et al. provided supportive evidence towards a less-than-exponential decline kinetic (Guedeney et al., 1988; Doloy et al., 1991).

A possible mechanism could result from the fact, that lymphocytes carrying more than one aberration are less likely to survive a cell division. High tissue doses give rise to such cells, particularly so in cases of partial-body exposure or highly inhomogeneous distribution of the dose over the body (Bender et al., 1988a; see Awa et al., 1992 for a recent example). Findings from the patient studies support this assumption. When 'cells with at least one *dic*' are compared with *dic*/cell the decline of the former is considerably slower (Norman et al., 1966; Buckton et al., 1978). Further to the mechanisms mentioned above this

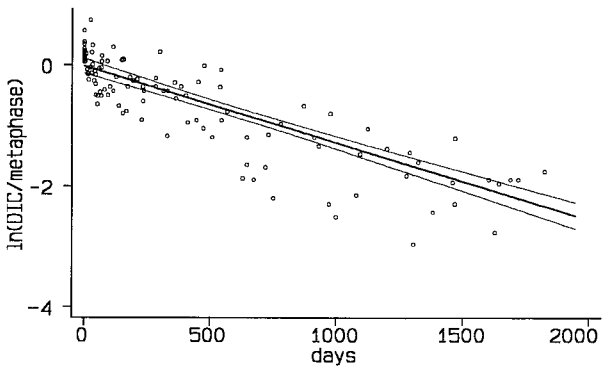

Figure 5. Weighted log–linear regression of combined original data (original data standardized to intercept = 0; weights = number of metaphases analysed; $R^2 = 0.87$, with 95% confidence bands for the conditional means).

observation could be explained in terms of different half-lives of various subfractions of human lymphocytes. Such differences have long been hypothesized. Sasaki and Miyata observed *dic* in peripheral blood lymphocytes in survivors 22 years after the atomic bomb assault in Japan (Sasaki and Miyata, 1968). The observed rates still correlated well with the individuals' distance to the hypocenter of the bomb. Randolph and Brewen calculated that in order to account for the correlation of persisting *dic* rates to the estimated initial exposure doses the average half-life of *dic* must be 3.6 (± 0.2) years (Randolph and Brewen, 1980).

Applying the purely exponential model the half-life derived in this paper thus would be overestimated for very short times after exposure but would be underestimated for long times. Furthermore, the decline derived from individuals exposed to high doses is likely to overestimate the decline in individuals exposed to environmental radiation only. It should be noted that the half-life estimate derived here is likely to be conservative with respect to the question at hand since longer half-times would increase the proportion of the background *dic* rate that would be attributable to background radiation.

Average Exposure of the General Population to Radiation $\overline{D}$

Table 1 lists various sources for radiation exposure of the general population. It is well known, that natural radiation varies markedly over different countries, but also within countries, depending predominantly on geological conditions and altitude. However, the tabulated values are supposed to be largely representative for the average population exposure in European countries as well as the USA.

We applied a quality factor of 25 to all densely ionizing fractions of the natural radiation. This is in partial contrast to the International Commission on Radiological Protection (ICRP), which uses energy-dependent quality factors between 5 and 20 for neutrons (ICRP, 1991), and about 10–20 for alpha-radiation (ICRP, 1973; ICRP, 1977). The International Commission on Radiation Units and Measurements (ICRU), in a joint task force with the ICRP, recently suggested an effective quality factor of 25 for both alpha radiation and neutrons, which should be applied grossly irrespective of the radiation energy (ICRU, 1986; see Kuni, 1994 for a comprehensive discussion). Using the conventional quality factor of 10, however, would reduce the total dose by no more than 20%. A principal problem is the definition of the 'critical organ' for the induction of *dic* (Pohl and Pohl-Rüling, 1982). In the absence of firm knowledge we referred to the effective dose concept (ICRP, 1991) for most of the sources of radiation. This seems to be justified for the penetrating components of irradiation (external and internal gamma-rays, neutrons and X-rays) and the rather homogeneously distributed incorporated radionuclides. An exception, however, is the extremely inhomogeneous exposure by radon inhalation which requires special consideration.

The main dose from radon and its decay products is delivered to the bronchial epithelium by alpha rays and it is generally estimated that the other compartments of the body receive only about 1% of the lung dose. The dose rate in nGy/h for soft tissues and a radon concentration C_{Rn} in Bq/m^3 according to the United Nations Scientific Committee on the Effects of Atomic Radiation (UNSCEAR, 1988) is $0.005 C_{Rn}$. For a mean indoor concentration of 49 Bq/m^3 and mean outdoor concentration of 14 Bq/m^3 in the former West Germany (Urban et al., 1985), a relation of 0.8 to 0.2 for the average time spent indoors and outdoors, and a *Q*-factor of 25, this results in a lymphoid tissue dose rate of 0.046 mSv/year. The other components in Table 1 add to a value of 3.24 mSv/year and radon would then represent 1.4% of the total lymphoid tissue dose.

This rather low exposure is in contradiction to the fact that persons living in atmospheres of elevated radon concentration show significantly increased chromosome aberrations in their peripheral lymphocytes (Brandom et al., 1978b; Stenstrand et al., 1979; Pohl and Pohl-Rüling, 1982; Pohl-Rüling and Fischer, 1983; Bauchinger et al., 1994; Bauchinger et al., 1996). The investigations of Stenstrand et al. (1979) allow an estimate of the dose–response for *dic*. The authors found a mean *dic* rate of 2.67×10^{-3} in 18 adults living in dwellings with radon contamination of their household water (6752 metaphases analysed). Their control value in nine persons was one *dic* and one C-ring in 4520 cells, i.e., a rate of 0.44×10^{-3} which corresponds to other published background values (Table 4). Only *dic* are considered here in the case of chronic exposure because only these are instable and can reach an equilibrium stage. We therefore take the average level of 0.544×10^{-3} derived below as a control value and receive a net excess *dic* rate of 2.13×10^{-3} which can be attributed to radon exposure.

The mean radon concentration measured in the dwellings and weighted by the number of persons involved can be calculated to be 1150 Bq/m^3. Assuming that the persons spend 0.5 of their time indoors, this corresponds to a mean concentration of 575 Bq/m^3 and an excess of 526 Bq/m^3 to the background of 49 Bq/m^3 assumed as normal in dwellings. Hence, if this concentration generates a *dic* rate of 2.13×10^{-3} and we assume linearity of the dose–response relation then a normal background radon level of 49 Bq/m^3 would correspond to a *dic* rate of 0.198×10^{-3} which means a proportion of 36% of the average background rate of 0.544×10^{-3} would be attributable to radon exposure. An analogous analysis of data published by Bauchinger et al. on 25 inhabitants of German homes with elevated indoor radon concentrations yields very simi-

Table 4. Published background rates for *dic* in human peripheral lymphocytes.

Number of individuals	Sex[a]	M1-control	Metaphases analysed	*dic*-rate	Reference
407		–	40,722	0.00020	Obe et al., 1977
71	45 m, 26 f	48 h cultures	14,164	0.00035	Obe and Herha, 1978
1793		48 h cultures	150,504	0.00054	Lloyd et al., 1980
140	140 m	48 h cultures, FPG in 99 of 140 cultures	23,831	0.00034	Obe et al., 1982
175	91 m, 84 f	48 h cultures (incl. 3 h of Colcemide)	17,500	0.00069	Gundy and Varga, 1983
109	94 m, 15 f	–	21,570	0.00009	Richardson et al., 1984
105	105 m	48 (incl. 4 h of Colcemide, FPG in 89 of 105 cultures)	10,300	0.00078	Tawn, 1987
253	253 m (?)[b]	48 h cultures (incl. 3 h of Colcemide), FPG in 50% of the cultures	27,249	0.00059[c]	De Jong et al., 1988
493	276 m, 218 f[d]	48 h cultures (incl. 2 h of Colcemide), FPG in parallel cultures	108,950	0.0016	Bender et al., 1988b, 1989, 1990
?[b]		48 h (incl 3 h of Colcemide)	8608	0.00035	Scheid et al., 1990
26		48 h culture (incl. 3 h Colcemide)	16,384	0.0009	Stephan and Oestreicher, 1989; Romm and Stephan, 1990
4	4 m	48 h culture (incl. 3 h Colcemide) FPG in sample slides coordinated experiment with 6 participating laboratories	11,969	0.0020	Lloyd et al., 1988a, 1992
20	10 m, 10 f	48 h culture (incl. 3 h Colcemide) FPG in sample slides (coordinated experiment with 6 participating laboratories)	60,000	0.00082	Lloyd et al., 1992
67	66 m, 1 f	FPG	35,500	0.00039	Braselmann et al., 1992
60		FPG?[b]	38,600	0.00040	Arndt et al., 1991; Wolf et al., 1991
25	16 m, 9 f	FPG	19,775	0.00046	(own data; Dannheim, 1996)

[a] m = male; f = female.
[b] Not specified by the authors.
[c] Incl. *centric r*.
[d] The numbers given for males and females actually add up to 494, instead of 493, as was stated by the authors.

lar estimates (0.191×10^{-3} *dic* attributable to a radon level of 49 Bq/m^3, analysis restricted to 19 adults in the sample (age 20 and above); 0.14×10^{-3} *dic* for the total sample; Bauchinger et al., 1994, 1996).

Because both these estimates are based on some uncertain assumptions about the stability of the radon concentration in Finish and German households, the duration of the respective exposure of the persons living there, and potential exposure-modifying factors such as the concentration of indoor fine particles we take as a final estimate the mean of the lymphocyte dose derived by UNSCEAR and by the Finnish and German measurements, i.e., 18.7% of the whole lymphoid dose is assumed to be caused by radon inhalation. This figure corresponds to a dose of 0.75 mSv/year (Table 1).

To allow for a discussion of the influence of radon exposure on the explained fraction of the background rate of *dic* we have repeated all calculations for an attributable proportion of 25% which would correspond to an estimate of 1 mSv/year to the lymphoid tissue (Figure 2, Tables 1 and 5B).

Background Rates of Dic

When sufficient numbers of metaphases are analysed, the variation of *dic* rates in control populations is fairly small. This numerical reproducibility in cohorts of both genders, various ages, and from different countries is particularly striking. With few exceptions published *dic* rates in unexposed controls are below 1/1000 metaphases (0.001 *dic*/metaphase), with the majority of published results ranging between 0.0003 and 0.0006 *dic* per metaphase (Table 4).

Much of the remaining variation in the background rates for *dic* is attributable to insufficient control of cell-cycle kinetics in culture and inappropriate selection of control subjects. A high proportion of M2 metaphases in the analysis can bias the *dic* rate towards lower values (Richardson et al., 1984). The 'gold standard' to control for the rate of second metaphases in culture is the application of FPG staining for all slides (Perry and Wolff, 1974). However, rather than routinely applying FPG staining to all cultures it might suffice to run parallel cultures with FPG to determine the donors' cell-cycle kinetics (Obe et

Table 5. Point estimates and error ranges in parameter estimates for α and Γ and respective consequences on the explained proportion of the background rate of *dic*.

A. With 18.7 % of background *dic*-rate attributable to indoor Radon-222

	Background rate of *dic* (with 95 % confidence limits)															
	0.000472						0.00054					0.000629				
α	Γ	−2 s.e.	−1 s.e.	p.e.	+1 s.e.	+2 s.e.	−2 s.e.	−1 s.e.	p.e.	+1 s.e.	+2 s.e.	−2 s.e.	−1 s.e.	p.e.	+1 s.e.	+2 s.e.
+2 s.e.	1	1	1	0.97	0.93	0.96	0.92	0.88	0.85	0.81	0.82	0.79	0.75	0.73	0.70	
+1 s.e.	1	1	0.96	0.92	0.89	0.91	0.87	0.84	0.81	0.78	0.78	0.75	0.72	0.69	0.67	
p.e.	0.99	0.95	0.91	0.88	0.84	0.87	0.83	***0.80***	0.77	0.74	0.74	0.71	0.68	0.66	0.63	
−1 s.e.	0.94	0.90	0.86	0.83	0.80	0.82	0.79	0.75	0.73	0.70	0.70	0.67	0.65	0.62	0.60	
−2 s.e.	0.89	0.85	0.82	0.78	0.75	0.77	0.74	0.71	0.68	0.66	0.66	0.64	0.61	0.59	0.57	

B. With 25 % of background *dic*-rate attributable to indoor Radon-222

	Background rate of *dic* (with 95 % confidence limits)															
	0.000472						0.00054					0.000629				
α	Γ	−2 s.e.	−1 s.e.	p.e.	+1 s.e.	+2 s.e.	−2 s.e.	−1 s.e.	p.e.	+1 s.e.	+2 s.e.	−2 s.e.	−1 s.e.	p.e.	+1 s.e.	+2 s.e.
+2 s.e.	1	1	1	1	1	1	1	0.96	0.92	0.89	0.90	0.86	0.82	0.79	0.76	
+1 s.e.	1	1	1	1	0.97	0.99	0.95	0.91	0.88	0.85	0.85	0.82	0.78	0.75	0.73	
p.e.	1	1	0.99	0.95	0.92	0.94	0.90	***0.87***	0.83	0.80	0.81	0.78	0.75	0.72	0.69	
−1 s.e.	1	0.98	0.94	0.90	0.87	0.89	0.86	0.82	0.79	0.76	0.77	0.74	0.71	0.68	0.65	
−2 s.e.	0.97	0.93	0.89	0.85	0.82	0.84	0.81	0.78	0.75	0.72	0.73	0.70	0.67	0.64	0.62	

s.e. = standard error; p.e. = point estimate; $\pm n$ s.e. = point estimate $\pm n^*$ standard error; α = linear dose coefficient; Γ = decline coefficient; (central estimate in ***bold italics***).

al., 1982; Tawn, 1987; Bender et al., 1988b; De Jong et al., 1988; Lloyd et al., 1988a, 1992). Adhering strictly to 48-h cultures (including a few hours of colcemid treatment, which further reduces the time for cell division in culture) can considerably reduce the proportion of M2 metaphases in the analysis, but is less reliable as compared to the FPG method (Wagner et al., 1983).

On the other hand, careful attention must be given to the selection of control subjects, particularly with respect to exposure to ionizing radiation from occupational or other sources. Bender et al. selected volunteers from the Brookhaven National Laboratory workforce, 144 of which were classified 'radiation workers' (defined as 'badged to record occupational exposure'). Radiation worker status of another 28 workers was 'unknown'. Both groups together comprised about 50% of the 'unexposed controls' in this sample. Despite this obvious source for bias the authors put forward one of the highest 'background' rates ever reported (0.00163 *dic*/metaphase, Bender et al., 1988b). Considerable contamination of this sample is evident from the extremely wide range of values for individual *dic* rates (0.0 to 0.016 per metaphase; Bender et al., 1990) as well as from a highly significant overdispersion of the intercellular *dic* distribution (6 metaphases with two *dic* observed, none expected).

Tawn found high rates of *dic* in a subset of new entrants from BNFL Sellafield who were on long-term medication for chronic medical conditions (Tawn, 1987). No information is provided as to the specific diagnoses, but among the most prevalent chronic conditions in these age groups are osteoskeletal pain syndromes which could well have given rise to the individuals' cumulative dose from diagnostic radiology. If individuals with potential prior exposure to clastogens were excluded from the analysis, the background rate for *dic* decreased to 0.00061 (66 individuals). A similiar selection bias might have added to a relatively high background level observed in a study of Hungarian blood donors and individuals undergoing a pre-employment medical investigation (Gundy and Varga, 1983). At the time of the sampling routine annual photofluorography screening of the population was performed in Hungary. This technique was later abandoned in most countries due to the relatively high patient doses associated with it (Heuck and Hofmann, 1984).

The high *dic*-rate observed by Lloyd et al. is based on pooled results from six laboratories (about 12,000 cells) from four donors (Lloyd et al., 1988a; Lloyd et al., 1992). Unexpectedly, the *dic* rates obtained for blood samples irradiated with up to 50 mGy were lower than this background rate. Significant variation was observed both among the participating laboratories (about threefold) and the four donors (2.5-fold). One of the donors had a markedly higher background *dic* rate, and moreover, four metaphases with two *dic* were observed in 15,000 of his metaphases (pooled data for 0, 3, 5, 10, and 20 mGy, respectively). Since lymphocytes from this donor did not show increased

radiation sensitivity an undocumented previous exposure appears to be the most likely explanation for the unusual *dic* rate observed. In a much larger second experiment conducted by the same group of investigators the background *dic* rate observed in 60,000 cells from 20 donors were 60% lower than in the previous experiment. Irradiation with 30 mGy already doubled the background level (Lloyd et al., 1992).

Reports on control populations that do not present *dic* results separately but rather group *dic* together with rings, translocations, and 'abnormal chromosomes' (Galloway et al., 1986) are useless for the determination of the background rate for *dic*. This is, however, not always appreciated (Bender et al., 1988b).

For the purpose of this paper, published data on the background rates for *dic* were combined using a weighted average with the number of metaphases analysed used as weights (Table 4). Further to studies with evidence for contaminated samples we excluded data from experiments without M1/M2 discrimination (Obe et al., 1977; Richardson et al., 1984), as well as sources where only combined rates for *dic* and *centric r* were reported (De Jong et al., 1988). The weighted average of the remaining nine studies was 0.54 *dic*/1000 (95% CI based on a Poisson distribution: 0.472–0.629) metaphases. These studies altogether represent 367.366 metaphases from more than 2200 donors.

The Radiation-Induced Proportion of the Background Rate for Dic

Using numerical values of the model parameters derived above, Eq. (3) yields the *dic* rate which would be expected if radiation were in fact the only clastogen capable of inducing *dic* in human peripheral blood of unexposed controls *in vivo* (Eq. (5)).

$$y_s = \frac{5.02 \times 10^{-5} * 0.011}{1.285 \times 10^{-3}}$$

$$= 4.30 \times 10^{-4} \left[\frac{dic/(\text{metaphase} * \text{mSv}) * \text{mSv}/d}{1/d} \right]$$

$$= 4.30 \times 10^{-4} \left[\frac{dic}{\text{metaphase}} \right] \quad (5)$$

With a weighted average of the data on the background aberration rate in unexposed controls of 5.4×10^{-4} *dic*/metaphase we obtain the fraction of 'explained' background rate:

$$4.3 \times 10^{-4}/5.4 \times 10^{-4} = 80.0\%$$

Hence, according to this model 80.0% of the *dic* rate in unexposed controls is explained in terms of average radiation exposure from natural and man-made sources. The explained fraction of the background rate of *dic* depends on the numerical estimates for the linear dose–response coefficient and the decline constant as well as on the total annual dose to the lymphoid tissue (Table 5).

Interpreting this value with respect to the question of specificity of the *dic*-assay for the detection of radiation exposure, it should be considered that parameter estimates were conservative in several independent instances.

–Co-60 data were used to represent low-LET radiation such as terrestrial gamma radiation and the gamma-emitting natural radionuclides (K-40, C-14). In fact, a considerable proportion of the 'low energy' component of the natural background radiation has considerably higher LET than Co-60 gamma rays. Likewise, medical radiation, by far the most common man-made exposure in industrialized countries mainly uses X-rays in the 60–80 keV energy range. In mammography even lower energies (around 30 keV) are used. In the majority of the X-ray experiments (Table 2), however, higher radiation energies and hence lower LET radiation was used.

–Medical radiation dose is likely to be underestimated. For Germany 1.5 mGy were published as an official estimate for the average exposure of the general population. Other sources reported doses as high as 2.06 mGy/year (Adzersen, 1991). Data on the frequency of medical X-ray application are based mainly on statistics related to health plans and reimbursement. They are thus likely to be incomplete (repeated films, technically unsatisfactory films are not counted). Another uncertainty concerns the patient dose. Results from phantom measurements are used to derive population doses from the estimated frequencies of various X-ray investigations. These laboratory measurements are not only based on standard body mass, size, and anatomical features but do moreover assume 'good practice'. Hence patient dose of a particular investigation is minimized. This, however, is not realistic in clinical practice.

On the other hand, about 50% of the patients undergoing X-ray investigations are over age 65 (Bernhardt et al., 1995), whereas many of the unexposed controls studied to determine the background *dic* rate are younger. However, in earlier years, children and young adults had considerable exposure doses due to radiological diagnostic for hip dysplasia, scoliosis, and pre-occupational screening (see Adzersen, 1991 for a review).

Although Germany is among the leading nations in terms of average exposure to ionizing radiation from medical sources, similiar figures are reported from other European countries (Schibilla, 1995) as well as Japan and the USA (Adzersen, 1991).

–There is considerable evidence from cytogenetic studies, that the contribution of Radon-222 to lymphocyte dose and, hence, to the background rate of dicentric chromo-

somes, is actually higher than assumed in our estimate (Brandom et al., 1978b; Stenstrand et al., 1979; Pohl and Pohl-Rüling, 1982; Pohl-Rüling and Fischer, 1983; Bauchinger et al., 1994, 1996). The data of Stenstrand et al. and Bauchinger et al. consistently suggest a percentage well above the 18.7% assumed in this paper.

–There is considerable evidence that the decline of *dic* in peripheral blood lymphocytes is actually slower than derived herein, and, particularly for longer periods of time, possibly considerably so.

–The background rates reported in the literature might not be representative for all segments of the population. For instance, little is known about the *dic* rate in unexposed children. There is some indication, however, that background *dic* rates are actually lower in children than in adults (Patil et al., 1972; Prieur et al., 1988; Bender et al., 1989; Bauchinger, 1995). In our laboratory we observed a *dic*-rate of only 0.1×10^{-3} metaphases in a sample of 10 children (five boys, five girls, 9650 metaphases analysed) which is considerably lower than our laboratory control for adults (Dannheim, 1996; Table 4). It is noteworthy that lower background rates for young children are predicted by the model presented in this analysis. According to the parameters derived herein, the background rate for adults would be representative for children over approximately 10 to 11 years (Figure 2).

Conclusion

In a model analysis the background rate of *dic* in the general adult population appears to be almost exclusively attributable to the clastogenic action of ionizing radiation from natural and man-made sources.

The sum of the clastogenic action from all other sources combined, including smoking, alcohol, and drugs could hence at best account for only a very small proportion of the background rate. It is equally likely that the background rate of *dic* is induced exclusively by ionizing radiation.

Hence in this approach *dic* appear to be sufficiently specific for ionizing radiation to allow for discrimination of excess radiation exposure from exposures to other environmental mutagens and clastogens in the general population.

As a consequence, *dic* appear appropriate as a biomarker to assess previous exposure to ionizing radiation down to the low dose range which is of particular interest in environmental epidemiology.

Acknowledgments

We are indebted to Dipl.-Biol. Anna Heimers and Dipl.-Biol. Heike Schröder, University of Bremen, for intense discussion and many useful comments on the manuscript.

References

Abbatt J.D., Bora K.C., Quastel M.R. and Lefkovitch L.P. International reference study on the identification and scoring of human chromosome aberrations. *Bull. World Health Organ.* 1974: 50: 373–388.

Adzersen K.H. Medizinische Strahlenbelastung in der Bundesrepublik Deutschland, Möglichkeiten der Dosisreduktion. In: Köhnlein W., Kuni H., Lengfelder E., Scholz R. and Schmitz-Feuerhake I. (Eds.), Berichte des Otto Hug Strahleninstitutes. MMV Medizin Verlag GmbH, München, 1991.

Arbor A. Persistant chromosomal aberrations following radioiodine therapy. *J. Nucl. Med.* 1964: 5: 840–850.

Arndt D., Wolf U., Fender H. and Reschofsky I. In: Bundesgesundheitsamt (Ed.), bga-Tätigkeitsbericht, Ergebnisse strahlenschutzmedizinischer Untersuchungen an ukrainischen Ferienkindern und begleitenden Erwachsenen, Berlin. 1991: pp. 36–38.

Awa A.A., Nakano M., Ohtaki K., Kodama Y., Lucas J. and Gray J. Factors that determine the *in vivo* dose–response relationship for stable chromosome aberrations in A-bomb survivors. *J. Radiat. Res. Tokyo* 1992: 33 (Suppl): 206–214.

Barcinski M.A., DoCeu M., Abreu A., Carlos J., DeAlmeida J.C.C., Naya J.M., Fonseca L.G. and Castro L.E. Cytogenetic investigation in a Brazilian population living in an area of high natural radioactivity. *Am. J. Hum. Genet.* 1975: 27: 802–806.

Barquinero J.F., Barrios L., Caballin M.R., Miro R., Ribas M., Subias A. and Egozcue, J. Cytogenetic analysis of lymphocytes from hospital workers occupationally exposed to low levels of ionizing radiation. *Mut. Res.* 1993: 286: 275–279.

Bauchinger M. Quantification of low-level radiation exposure by conventional chromosome aberration analysis. *Mut. Res.* 1995: 339: 177–189.

Bauchinger M., Schmid E. and Hug O. The relevance of chromosome aberration yields for biological dosimetry after low-level occupational irradiation. In: Advances in Physical and Biological Radiation Detectors. International Atomic Energy Agency (IAEA), Vienna. 1971: pp. 623–632.

Bauchinger M., Schmid E. and Dresp J. Calculation of the dose-rate dependence of the dicentric yield after Co gamma-irradiation of human lymphocytes. *Int. J. Radiat. Biol.* 1979: 35: 229–233.

Bauchinger M., Kolin-Gerresheim J., Schmid E. and Dresp J. Chromosome analyses of nuclear-power plant workers. *Int. J. Radiat. Biol.* 1980: 38: 577–581.

Bauchinger M., Kuehn H., Dresp J., Schmid E. and Streng S. Dose–effect relationship for 14.5 MeV (d + T) neutron-induced chromosome aberrations in human lymphocytes irradiated in a man phantom. *Int. J. Radiat. Biol.* 1983a: 43: 571–578.

Bauchinger M., Schmid E., Streng S. and Dresp J. Quantitative analysis of the chromosome damage at first division of human lymphocytes after ^{60}Co gamma-irradiation. *Rad. Environ. Biophys.* 1983b: 22: 225–229.

Bauchinger M., Schmid E., Braselmann H., Willich N. and Clemm C. Time–effect relationship of chromosome aberrations in peripheral lymphocytes after radiation therapy for seminoma. *Mut. Res.* 1989: 211: 265–272.

Bauchinger M., Schmid E., Braselmann H. and Kulka U. Chromosome aberrations in peripheral lymphocytes from occupants of houses with elevated indoor radon concentrations. *Mut. Res.* 1994: 310: 135–142.

Bauchinger M., Braselmann H., Kulka U., Huber R. and Georgiadou-Schumacher V. Quantification of FISH-painted chromosome aberrations after domestic radon exposure. *Int. J. Radiat. Biol.* 1996: 70: 657–663.

Bauer B., Bernhardt J. and Tsavachidis C. In: Bundesamt für Strahlenschutz (Ed.), Jahresbericht 1992 [ISSN 0940-7650]. Bestimmung der Strahlenexposition der Bevölkerung durch die Röntgendiagnostik. Teil 1: Ermittlungen zur Häufigkeit. BFS, Salzgitter. 1993: pp. 60–62.

Bender M.A. and Gooch P.C. Persistant chromosome aberrations in irradiated human subjects. *Radiat. Res.* 1962: 16: 44–53.

Bender M.A. and Gooch P.C. Persistant chromosome aberrations in irradiated human subjects: II. Three and one-half year investigation. *Radiat. Res.* 1963: 18: 389–396.

Bender M.A. and Gooch P.C. Somatic chromosome aberrations induced by human whole-body irradiation: The 'Recuplex' criticality accident. *Radiat. Res.* 1966: 29: 568–582.

Bender M.A., Griggs H.G. and Bedford J.S. Mechanisms of chromosomal aberration production: III. Chemicals and ionizing radiation. *Mut. Res.* 1974: 23: 197–212.

Bender M.A., Awa A.A., Brooks A.L., Evans H.J., Groer P.G., Littlefield L.G., Pereira C., Preston R.J. and Wachholz B.W. Current status of cytogenetic procedures to detect and quantify previous exposures to radiation. *Mut. Res.* 1988a: 196: 103–159.

Bender M.A., Preston R.J., Leonard R.C., Pyatt B.E., Gooch P.C. and Shelby M.D. Chromosomal aberration and sister-chromatid exchange frequencies in peripheral blood lymphocytes of a large human population sample. *Mut. Res.* 1988b: 204: 421–433.

Bender M.A., Preston R.J., Leonard R.C., Pyatt B.E. and Gooch P.C. Chromosomal aberration and sister-chromatid exchange frequencies in peripheral blood lymphocytes of a large human population sample: II. Extension of age range. *Mut. Res.* 1989: 212: 149–154.

Bender M.A., Preston R.J., Leonard R.C., Pyatt B.E. and Gooch P.C. On the distributions of spontaneous chromosomal aberrations in human peripheral blood lymphocytes in culture. *Mut. Res.* 1990: 244: 215–220.

Bernhardt J.H., Veit R. and Bauer B. Erhebungen zur effektiven Dosis und zur Kollektivdosis bei der Röntgendiagnostik in den alten Bundesländern. In: Bundesministerium für Umwelt, Naturschutz und Reaktorsicherheit (Ed.), Strahlenexposition in der medizinischen Diagnostik. Veröffentlichungen der Strahlenschutzkommission (SSK) Band 30. Gustav Fischer Verlag, Stuttgart, Jena, New York. 1995: pp. 180–204.

Bianchi M., Bianchi N.O., Brewen J.G., Buckton K.E., Fabry L., Fischer P., Gooch P.C., Kucerova M., Leonard A., Mukherjee R.N., Mukherjee U., Nakai S., Natarajan A.T., Obe G., Palitti F., Pohl-Rüling J., Schwarzacher H.G., Scott D., Sharma T., Takahashi E., Tanzarella C. and van Buul P.P.W. Evaluation of radiation-induced chromosomal aberrations in human peripheral blood lymphocytes *in vitro*. *Mut. Res.* 1982: 96: 233–242.

Blackwell N., Stevenson A.C. and Wiernik G. Chromosomal findings in patients treated with small doses of Iodine-131. *Mut. Res.* 1974: 25: 397–402.

Bloom A.D. and Tjio J.H. *In vivo* effects of diagnostic X-irradiation on human chromosomes. *N. Engl. J. Med.* 1964: 270: 13411–11344.

Bocian E., Ziemba-Zak B., Rosiek O. and Sablinski J. Chromosome aberrations in human lymphocytes exposed to tritiated water *in vitro*. *Curr. Top. Radiat. Res. Q.* 1977: 12: 168–181.

Bonassi S., Abbondandolo A., Camurri L., Dal-Pra L., De-Ferrari M., Degrassi F., Forni A., Lamberti L., Lando C., Padovani P., Sbrana I., Vecchio D. and Puntoni R. Are chromosome aberrations in circulating lymphocytes predictive of future cancer onset in humans? Preliminary results of an Italian cohort study. *Cancer Genet. Cytogenet.* 1995: 79: 133–135.

Boyd E., Buchanan W.W. and Lennox B. Damage to chromosomes by therapeutic doses of radioiodine. *Lancet* 1961: 977–978.

Boyd E., Ferguson-Smith M.A., McDougall I.R. and Grieg W.R. Chromosome breakage in human peripheral lymphocytes after radioactive iodine (125J) treatment. *Radiat. Res.* 1974: 57: 482–487.

Brandom W., Bloom A., Archer P. and Bistline R. Chronic irradiation effects in blood lymphocyte chromosomes of plutonium workers (abstract at the 2nd International Conference on Environmental Mutagens, July 11th–15th, 1977, Edinburgh). *Mut. Res.* 1978a: 53: 129–286.

Brandom W., Saccamanno G., Archer V.E., Archer P.G. and Bloom A.D. Chromosome aberrations as a biological dose–response indicator of radiation exposure in uranium miners. *Radiat. Res.* 1978b: 76: 159–171.

Braselmann H., Bauchinger M. and Schmid E. Cell survival and radiation induced chromosome aberrations; I. Derivation of formulae for the determination of transmission and survival parameters of aberrations. *Rad. Environ. Biophys.* 1986: 25: 243–251.

Braselmann H., Schmid E. and Bauchinger M. Chromosome analysis in a population living in an area of Germany with the highest fallout deposition from the Chernobyl accident. *Mut. Res.* 1992: 283: 221–225.

Brewen J.G. and Luippold H.E. Radiation-induced human chromosome aberrations: *In vitro* dose rate studies. *Mut. Res.* 1971: 12: 305–314.

Brewen J.G., Preston R.J. and Littlefield L.G. Radiation-induced chromosome aberration yields following an accidental whole-body exposure to ^{60}Co gamma-rays. *Radiat. Res.* 1972: 49: 647–656.

Brown J.K. and McNeill J.R. Aberrations in leukocyte chromosomes of personnel occupationally exposed to low levels of radiation. *Radiat. Res.* 1969: 40: 534–543.

Buckton K.E. and Pike M.C. Chromosome investigations on lymphocytes from irradiated patients: Effect of time in culture. *Nature* 1964: 202: 714–715.

Buckton K.E., Hamilton G.E., Paton L. and Langlands A.O. Chromosome aberrations in irradiated ankylosing spondylitis patients. In: Evans H.J. and Lloyd D.C. (Eds.), Mutagen-induced chromosome damage in man. Edinburgh University Press, Edinburgh. 1978: pp. 142–150.

Burkhardt J. and Tillmanns G. Zusammenfassende Bewertung der Strahlenexposition der Bevölkerung. In: Bundesamt für Strahlenschutz; Fachbereich Strahlenhygiene/Institut für Strahlenhygiene (Eds.), Daten zur Umgebungs- und Umweltradioaktivität in der Bundesrepublik Deutschland in den Jahren 1990–1992 [report BFS-ISH-162/93]. ISH, Neuherberg. 1993: pp. 73–76.

Cantolino S.J., Schmickel R.D., Ball M. and Cisar C.F. Persistant chromosomal aberrations following radioiodine therapy for thyrotoxicosis. *N. Engl. J. Med.* 1966: 275: 739–745.

Carrano V.A. and Heddle J.A. The fate of chromosome aberrations. *J. Theor. Biol.* 1973: 38: 289–304.

Chee C.A.K. and Ilbery P.L.T. Dose response relationships between chromosome damage and absorbed radiation. *Australas. Radiol.* 1975: 19: 60–71.

Coppola M., Vulpis N. and Bertoncello G. Relative frequency of acentrics to dicentrics caused by radiation and by chemical action of human lymphocytes. *Mut. Res.* 1986: 174: 75–78.

Crossen P.E. and Morgan W.F. Analysis of human lymphocyte cell cycle time in culture measured by sister chromatid differential staining. *Exp. Cell Res.* 1977: 104: 453–457.

Dannheim B. Retrospective Dose Estimation of Children. In: Heinemann G. and Pfob H. (Eds.), Strahlenbiologie und Strahlenschutz. Fachverband für Strahlenschutz e.V., Hannover. 1996: pp. 172–176.

Das B.C. and Sharma T. The fate of X-ray-induced chromosome aberrations in blood lymphocyte culture. *Mut. Res.* 1987: 176: 93–104.

De Jong G., van Sittert N.J. and Natarajan A.T. Cytogenetic monitoring of industrial populations potentially exposed to genotoxic materials and of control populations. *Mut. Res.* 1988: 204: 451–464.

De la Chapelle A., Oka M., Rekonen A. and Ruotsi A. Chromosome damage after intra-articular injections of radioactive yttrium. *Ann. Rheum. Dis.* 1972: 31: 508–512.

Doloy M.T., Malarbet J.L., Guedeney G., Bourguignon M., Leroy A., Reillaudou M. and Masse R. Use of unstable chromosome aberrations for biological dosimetry after the first postirradiation mitosis. *Radiat. Res.* 1991: 125: 141–151.

Dolphin G.W. A review of *in vitro* dose–effect relationships. In: Evans H.J. and Lloyd D.C. (Eds.), Mutagen-induced chromosome damage in man. Edinburgh University Press, Edinburgh. 1978.

Dolphin G.W., Bolton D., Humphreys D.L.O., Speight D.L. and Stradling G.N. Biological and physical dosimetry after a radiation accident [July 11]. *Nature* 1970: 227: 165.

Dolphin G.W. and Purrott R.J. Use of radiation-induced chromosome aberrations in human lymphocytes for dosimetry. In: Advances in Physical and Biological Radiation Detectors. International Atomic Energy Agency (IAEA), Vienna. 1971: pp. 611–622.

Dolphin G.W., Lloyd D.C. and Purrott R.J. Chromosome aberration analysis as a dosimetric technique in radiological protection. *Health Phys.* 1973: 25: 7–15.

Dvoreckij L.I., Pokrovskaja V.N. and Melnikova A.E. Zur Frage der biologischen Dosimetrie bei akuter Bestrahlung des Menschen (translated into German). *Radiobiol. Radiother.* 1971: 2: 233–241.

Edwards A.A., Lloyd D.C., Prosser J.S., Finnon P. and Moquet J.E. Chromosome aberrations induced in human lymphocytes by 8.7 MeV protons and 23.5 MeV helium-3 ions. *Int. J. Radiat. Biol.* 1986: 50: 137–145.

El-Alfi O.S., Ragab A.S. and Eassa E.-H.M. Detection of radiation damage in exposed personnel by chromosome study. *Br. J. Radiol.* 1967: 40: 760–764.

Evans H.J., Buckton K.E., Hamilton G.E. and Carothers A. Radiation-induced chromosome aberrations in nuclear dockyard workers. *Nature* 1979: 277: 531–534.

Fabry L. Cytogenetic damage induced in human lymphocytes by low doses of ^{60}Co gamma rays delivered at high and low dose rates. *Acta Radiol. Oncol.* 1986: 25: 143–146.

Fabry L., Leonard A. and Wambersie A. Induction of chromosome aberrations in Go human lymphocytes by low doses of ionizing radiations of different quality. *Radiat. Res.* 1985: 103: 122–134.

Galloway S.M., Berry P.K., Nichols W.W., Wolman S.R., Soper K.A., Stolley P.D. and Archer P. Chromosome aberrations in individuals occupationally exposed to ethylene oxide, and in a large control population. *Mut. Res.* 1986: 170: 55–74.

Gensicke F., Solle M., Laussmann D., Fender H., Bruening J., Conrady J., Klatt R. and Arndt D. Strahlenbiologische Untersuchungen an Beschäftigten eines Kernkraftwerkes. *Bundesgesundheitsblatt* 1991: 11: 513–517.

Golob E., Fischer P. and Kunze-Mühl E. Einfluß der Kulturdauer auf strahleninduzierte Chromosomenaberrationen menschlicher Lymphocyten des peripheren Blutes. *Strahlentherapie* 1969: 137: 63–67.

Goodhead D.T. and Nikjoo H. Track structure analysis of ultrasoft X-rays compared to high- and low-LET radiations. *Int. J. Radiat. Biol.* 1989: 55: 513–529.

Goodman R.M., Rechheimer N.S., Miller F., Miller R. and Zartman, D. Chromosomal alteration in three age groups of human females. *Am. J. Med. Sci.* 1969: 258: 26–34.

Guedeney G., Grunwald D., Malarbet J.L. and Doloy M.T. Time dependence of chromosomal aberrations induced in human and monkey lymphocytes by acute and fractionated exposure to ^{60}Co. *Radiat. Res.* 1988: 116: 254–262.

Gumrich K., Virsik-Peuckert R.P. and Harder D. Temperature and the formations of radiation-induced chromosome aberrations; I. The effect of irradiation temperature. *Int. J. Radiat. Biol.* 1986: 49: 665–672.

Gundy S. and Varga L. Chromosomal aberrations in healthy persons. *Mut. Res.* 1983: 120: 187–191.

Hagmar L., Brögger A., Hansteen Inge-L., Heim S., Högstedt B., Knudson L., Lambert B., Linnainmaa K., Mitelman F., Nordenson I., Reuterwall C., Salomaa S., Skerfving S. and Sorsa M. Cancer risk in humans predicted by increased levels of chromosomal aberrations in lymphocytes: Nordic Study Group on the Health Risk of Chromosome Damage. *Cancer Res.* 1994: 54: 2919–2922.

Heimers A., Schröder H., Lengfelder E. and Schmitz-Feuerhake I. Chromosome aberration analysis in aircrew members. *Radiation Protection Dosimetry* 1995: 60: 171–175.

Heuck F.H.W. and Hofmann F.W. Bedeutung eines Großformat-Bildverstärkers für die Reihenuntersuchung der Thoraxorgane. *Radiologie* 1984: 24 (3): 139–143.

Hoegerman S.F., Cummins H.T., Greco I. and Bronec J.F. Chromosome aberrations in lymphocytes from patients with low body burdens of ^{226}Ra. *Health Phys.* 1975: 28: 820–823.

Hölzer, F. Natürliche Strahlenexposition. In: Bundesamt für Strahlenschutz; Fachbereich Strahlenhygiene/Institut für Strahlenhygiene (Eds.), Daten zur Umgebungs- und Umweltradioaktivität in der Bundesrepublik Deutschland in den Jahren 1990–1992 [report BFS-ISH-162/93] ISH, Neuherberg. 1993: pp. 5–8.

Hoffmann W., Dannheim B., Grell-Büchtmann I., Heimers A., Nahrmann A., Schröder H., Schmitz-Feuerhake I. and Tomalik P. Chromosomenaberrationsanalyse zur retrospektiven Dosisermittlung nach Exposition mit ionisierender Strahlung: Biologische Dosimetrie. *Bioforum* 1991: 10: 381–385.

Holmberg M. On the time course of the interactions between DNA breaks in the production of a radiation-induced chromosome exchange aberration. *Mut. Res.* 1990: 232: 267–272.

Holmberg M. and Gumauskas E. The role of short-lived DNA lesions in the production of chromosome exchange aberrations. *Mut. Res.* 1986: 160: 221–229.

Honda T., Kamada N. and Bloom A.D. Chromosome aberrations and culture time. *Cytogenetics* 1969: 8: 117–124.

Hulka B.S. Overview of biological markers. In: Hulka B.S., Wilcosky T.C. and Griffith J.D. (Eds.), Biological markers in epidemiology. Oxford University Press, New York, Oxford. 1990: pp. 3–15.

ICRP (International Commission on Radiological Protection) Data for protection against ionizing radiation from external sources: Supplement to ICRP 15, Recommendations of the International Commission on Radiological Protection. Publication 21. Pergamon Press, Oxford, New York, 1973.

ICRP (International Commission on Radiological Protection). Recommendations of the International Commission on Radiological Protection. Publication 26. Annals of the ICRP Vol. 1, No.3. Pergamon Press, Oxford, New York, 1977.

ICRP (International Commission on Radiological Protection). Recommendations of the International Commission on Radiological Protection. Publication 60. Annals of the ICRP Vol. 21, No. 1–3. Pergamon Press, Oxford, New York, Frankfurt, 1991.

ICRU (International Commission on Radiation Units and Measurements). The quality factor in radiation protection. Report of a joint task force group of the ICRP and ICRU to the ICRP and ICRU. ICRU report 40, Bethesda, Maryland, USA, 1986.

Jha A.N. and Sharma T. Enhanced frequency of chromosome aberrations in workers occupationally exposed to diagnostic X-rays. *Mut. Res.* 1991: 260: 343–348.

Kumagai E., Tanaka R., Kumagai T., Onomichi M. and Sawada S. Effects of long-term radiation exposure on chromosomal aberrations in radiological technologists. *J. Radiat. Res.* 1990: 31: 270–279.

Kuni H. Niedrige Strahlendosen und Gesundheit der Arbeitnehmer. Expertise mit besonderer Berücksichtigung der Arbeitsbedingungen in der Anlage Schacht Konrad. In: Köhnlein W., Kuni H., Lengfelder E., Scholz R. and Schmitz-Feuerhake I. (Eds.), Berichte des Otto Hug Strahleninstitutes. MMV Medizin-Verlag, München. 1994: p. 168.

Lea D.E. Actions of radiations on living cells. Cambridge University Press, Cambridge, 1956.

Lea D.E. and Catcheside D.G. Induction by radiation of chromosome aberrations in Tradescantia. *J. Genet.* 1942: 44: 216–222.

Liniecki J., Bajerska A. and Andryszek A. Chromosomal aberrations in human lymphocytes irradiated *in vitro* from donors (males and females) of varying age. *Int. J. Radiat. Biol.* 1971: 19: 349–360.

Liniecki J., Bajerska A. and Wyszynska K. Dose–response relationships for chromosome aberrations in peripheral blood lymphocytes after

whole-and partial body irradiations; I. Effects immediately after irradiation. *Mut. Res.* 1983a: 110: 83–101.

Liniecki J., Bajerska A. and Wyszynska K. Dose–response relationships for chromosome aberrations in peripheral blood lymphocytes after whole-and partial body irradiations: II. Decline of aberration-carrying cells in blood with time post-exposure. *Mut. Res.* 1983b: 110: 103–110.

Littlefield L.G., Lever W.E., Miller F.L. and Goh K.O. Chromosome breakage studies in lymphocytes from normal women, pregnant women and women taking oral contraceptives. *Am. J. Obstet. Gynaecol.* 1975: 121: 976–980.

Lloyd D.C., Purrott R.J., Dolphin G.W., Bolton D., Edwards A.A. and Corp M.J. The relationship between chromosome aberrations and low LET radiation dose to human lymphocytes. *Int. J. Radiat. Biol.* 1975: 28: 75–90.

Lloyd D.C., Purrott R.J., Dolphin G.W., Horton P.W., Halnan K.E., Stewart Scott J. and Mair G. A comparison of physical and cytogenetic estimates of radiation dose in patients treated with iodine-131 for thyroid carcinoma. *Int. J. Radiat. Biol.* 1976: 30: 473–485.

Lloyd D.C., Purrott R. and Reeder E.J. The incidence of unstable chromosome aberrations in peripheral blood lymphocytes from unirradiated and occupationally exposed people. *Mut. Res.* 1980: 72: 523–532.

Lloyd D.C., Edwards A.A., Prosser J.S. and Corp M.J. The dose response relationship obtained at constant irradiation times for the induction of chromosome aberrations in human lymphocytes by cobalt-60 gamma rays. *Rad. Environ. Biophys.* 1984: 23: 179–189.

Lloyd D.C., Edwards A.A., Leonard A., Deknudt G., Natarajan A., Obe G., Palitti F., Tanzarella C. and Tawn E.J. Frequencies of chromosomal aberrations induced in human blood lymphocytes by low doses of X-rays. *Int. J. Radiat. Biol.* 1988a: 53: 49–55.

Lloyd D.C., Edwards A.A., Prosser J.S., Moquet J.E. and Finnon P. Doses in radiation accidents investigated by chromosome aberration analysis; XVII. A review of cases investigated, 1987 [NRPB-R217]. National Radiation Protection Board (NRPB), Chilton, Didcot, Oxon, 1988b.

Lloyd D.C., Edwards A.A., Leonard A., Deknudt G.L., Verschaeve L., Natarajan A.T., Darroudi F., Obe G., Palitti F., Tanzarella C. and Tawn E.J. Chromosomal aberrations in human lymphocytes induced *in vitro* by very low doses of X-rays. *Int. J. Radiat. Biol.* 1992: 61: 335–343.

Marlhens F., Al-Achkar W., Aurias A., Couturier J., Dutrillaux A.M., Gerbault-Sereau M., Hoffschir F., Lamoliatte E., Lefrancois D., Lombard M., Muleris M., Prieur M., Prod'homme M., Sabatier L., Viegas-Pequignot E., Volobouev V. and Dutrillaux B. The rate of chromosome breakage is age dependent in lymphocytes of adult controls. *Hum. Genet.* 1986: 73: 290–297.

McFee A.F. Chromosome aberrations in the leukocytes of pigs after half body or whole body irradiation. *Mut. Res.* 1977: 42: 395–400.

Moorhead P.S., Nowell P.C., Mellman W.J., Battips D.M. and Hungerford D.A. Chromosome preparations of leukocytes cultured from human peripheral blood. *Exp. Cell Res.* 1960: 20: 613–616.

Müller W.-U. and Streffer C. Biological indicators for radiation damage. *Int. J. Radiat. Biol.* 1991: 59: 863–873.

Natarajan A.T. Mechanisms for induction of mutations and chromosome alterations. *Environ. Health Perspect.* 1993: 101 (Suppl 3): 225–229.

Natarajan A.T., Darroudi F., Mullenders L.H.F. and Meijers M. The nature and repair of DNA lesions that lead to chromosomal aberrations induced by ionizing radiations. *Mut. Res.* 1986: 160: 231–236.

Neary G.J., Preston R.J. and Savage, J.R.K. Chromosome aberrations and the theory of RBE: III. Evidence from experiments with soft X-rays and a consideration of the effects of hard X-rays. *Int. J. Radiat. Biol.* 1967: 12: 317–345.

Neary G.J., Horgan V.J., Bance D.A. and Stretch A. Further data on DNA strand breakage by various radiation qualities. *Int. J. Radiat. Biol.* 1972: 22: 525–537.

Norman A., Sasaki M.S., Ottoman R.E. and Fingerhut A.G. Lymphocyte lifetime in women. *Science* 1965: 145: 745.

Norman A., Sasaki M.S., Ottoman R.E. and Fingerhut, A.G. Elimination of chromosome aberrations from human lymphocytes. *Blood* 1966: 27 (5): 706–713.

Obe G. and Herha J. Chromosomal aberrations in heavy smokers. *Hum. Genet.* 1978: 41: 259–263.

Obe G., Ristow H. and Herha, J. Chromosomal damage by alcohol *in vitro* and *in vivo*. In: Gross M.M. (Eds.), Alcohol intoxication and withdrawal-IIIa. Biological aspects of ethanol. Advances in experimental medicine and biology. Plenum Press, New York. 1977: pp. 47–70.

Obe G., Vogt H.-J., Madle S., Fahning A. and Heller W.D. Double-blind study on the effect of cigarette smoking on the chromosomes of human peripheral blood lymphocytes *in vivo*. *Mut. Res.* 1982: 92: 309–319.

Patil S.R., Ruddle F.H. and Lubs H.A. The lymphocyte as a dosimeter: Comparison of somatic chromosome aberrations in 522 newborn infants and 602 mothers. *Humangenetik* 1972: 14: 306–313.

Perry P. and Wolff S. New Giemsa method for the differential staining of sister chromatids. *Nature* 1974: 251: 156–158.

Pjatkin E.K. Biologische Dosimetrie durch Berechnung der aberranten Knochen-markmitosen bei akuten Strahlenschädigungen des Menschen. *Radiobiol. Radiother.* 1976: 4: 439–446.

Pohl E. and Pohl-Rüling J. Dose distribution in the human organism due to incorporation of radon and decay products as a base for epidemiological studies. In: Proceedings of the specialist meeting on the assessment of radon daughter exposure and related biological effects, Rome, March 3rd–8th 1980. Salt Lake City. 1982: pp. 84–91.

Pohl-Rüling J. and Fischer P. The dose–effect relationship of chromosome aberrations to alpha and gamma irradiation in a population subjected to an increased burden of natural radioactivity. *Radiat. Res.* 1979: 80: 61–81.

Pohl-Rüling J. and Fischer P. Chromosome aberrations in inhabitants of areas with elevated natural radioactivity. In: Ishihara T. and Sasaki M.S. (Eds.), Radiation-induced chromosome damage in man. Alan R. Liss, New York. 1983: pp. 527–560.

Pohl-Rüling J., Fischer P., Hass O., Obe G., Natarajan A.T., van Buul P.P.W., Buckton K.E., Bianchi N.O., Larramendy M., Kucerova M., Polikova Z., Leonard A., Fabry L., Palitti F., Sharma T., Binder W., Mukherjee R.N. and Mukherjee U. Effect of low-dose acute X-irradiation on the frequencies of chromosomal aberrations in human peripheral blood lymphocytes *in vitro*. *Mut. Res.* 1983: 110: 71–82.

Pohl-Rüling J., Fischer P., Lloyd D.C., Edwards A.A., Natarajan A.T., Obe G., Buckton K.E., Bianchi N.O., van Buul P.P.W., Das B.C., Daschil F., Fabry L., Kucerova M., Leonard A., Mukherjee R.N., Mukherjee U., Nowotny R., Palitti P., Polikova Z., Sharma T. and Schmidt W. Chromosomal damage induced in human lymphocytes by low doses of D-T neutrons. *Mut. Res.* 1986: 173: 267–272.

Pohl-Rüling J., Haas O., Brogger A., Obe G., Lettner H., Daschill F., Atzmueller C., Lloyd D.C., Kubiak R. and Natarajan A.T. The effect on lymphocytes chromosomes of additional radiation burden due to fallout in Salzburg (Austria) from the Chernobyl accident. *Mut. Res.* 1991: 262: 209–217.

Poncelet E., Leonard A., Leonard E.D. and Dutrillaux B. Biological dosimetry: Radiation-induced mitotic delay can lead to an underestimate of the part of the body exposed after non-uniform irradiation. *Strahlenther. Onkol.* 1988: 164: 542–543.

Popescu H.I. and Stefanescu D.T. Cytogenetic investigation of industrial workers occupationally exposed to gamma rays. *Radiat. Res.* 1971: 47: 562–570.

Prieur M., Al Achkar W., Aurias A., Couturier J., Dutrillaux A.M.,

Dutrillaux B., Fluery-Herard A., Gerbault-Seureau M., Hoffschir F., Lmoliatte E., Lefrancois D., Lombard M., Muleris M., Ricoul M., Sabatier L. and Viegas-Poquinot E. Acquired chromosome rearrangements in human lymphocytes: Effect of aging. *Hum. Genet.* 1988: 79: 147–150.

Purrott R.J. and Reeder E. The effect of changes in dose rate on the yield of chromosome aberrations in human lymphocytes exposed to gamma radiation. *Mut. Res.* 1976: 35: 437–444.

Purrott R.J., Vulpis N. and Lloyd D.C. The influence of incubation temperature on the rate of human lymphocyte proliferation *in vitro*. *Experientia* 1981: 37: 407–408.

Pyatkin E.K., Aleksandrov N.N., Vorobyev A.I., Petrova S.A. and Suskov I.I. Chromosome aberrations induced in human bone-marrow cells by therapeutical local gamma-irradiation, time and dose relationships. *Mut. Res.* 1972a: 16: 103–109.

Pyatkin E.K., Alexsandrov N.N., Vorobyev A.I., Petrova S.A. and Suskov I.I. Chromosome aberrations induced in human bone-marrow cells by therapeutical local gamma irradiation. *Mut. Res.* 1972b: 16: 103–109.

Ramalho A.T. and Nascimento A.C.H. The fate of chromosomal aberrations in 137Cs-exposed individuals in the Goiania radiation accident. *Health Phys.* 1991: 60: 67–70.

Randolph M.L. and Brewen J.G. Estimation of whole-body doses by means of chromosome aberrations observed in survivors of the Hiroshima A-bomb. *Radiat. Res.* 1980: 82: 393–407.

Richardson C.R., Howard C., Sheldon J., Wildgoose J. and Thomas M.G. The human lymphocyte *in vitro* cytogenetic assay: Positive and negative observations in 30,000 cells. *Mut. Res.* 1984: 141: 59–64.

Romm H. and Stephan G. Chromosome analysis—a routine method for quantitative radiation dose assessment. *Kerntechnik* 1990: 55: 219–225.

Rosenkranz W. and Veigl J. Sind die durch Erhöhung der Inkubationstemperatur ausgelösten strukturellen Chromosomenveränderungen auch Folgen eines gestörten DNA-Reparatursystems? In: Altmann H., Riklis E. and Slor H. (Eds.), DNA Repair and Late Effects. Publ. NRCN, Israel. 1980: pp. 297–303.

Sasaki M.S. and Norman A. Selection against chromosome aberrations in human lymphocytes. *Nature* 1967: 214: 502–503.

Sasaki M.S. and Miyata H. Biological dosimetry in atomic bomb survivors. *Nature* 1968: 220: 1189–1193.

Scheid W. and Traut H. Biological dosimetry after occupational exposure to ionizing radiation. *Naturwissenschaften* 1983: 70: 311–312.

Scheid W., Weber J. and Traut H. Chromosome aberrations induced in human lymphocytes by an X-radiation accident: Results of a 4-year postirradiation analysis. *Int. J. Radiat. Biol.* 1988: 54: 395–402.

Scheid W., Weber J. and Traut H. Biological and physical dosimetry after chronic occupational exposure to ionizing radiation: A comparative study. *Studia Biophysica* 1990: 138: 205–212.

Scheid W., Weber J., Traut H. and Gabriel H.W. Chromosome aberrations induced in the lymphocytes of pilots and stewardesses. *Naturwissenschaften* 1993: 80: 528–530.

Schibilla H. Die medizinische Strahlenexposition in der Röntgendiagnostik: Vergleich von Daten aus verschiedenen Mitgliedsstaaten der Europäischen Union. In: Bundesministerium für Umwelt, Naturschutz und Reaktorsicherheit, (Ed.), Strahlenexposition in der medizinischen Diagnostik. Veröffentlichungen der Strahlenschutzkommission (SSK) Band 30. Gustav Fischer Verlag, Stuttgart, Jena, New York. 1995: pp. 206–222.

Schmid E. and Bauchinger M. Ueber das zeitliche Verhalten strahleninduzierter Chromosomenaberrationen beim Menschen. *Mut. Res.* 1969: 8: 599–611.

Schmid E., Bauchinger M. and Hug O. Chromosomenaberrationen menschlicher Lymphocyten nach Röntgenbestrahlung *in vitro*: I. Qualitative und quantitative Aspekte der Dosis-Wirkungsbeziehung. *Mut. Res.* 1972: 16: 307–317.

Schmid E., Bauchinger M., Bunde E., Ferbert H.F. and von Lieven H. Comparison of the chromosome damage and its dose response after medical whole-body exposure to ^{60}Co gamma-rays and irradiation of blood *in vitro*. *Int. J. Radiat. Biol.* 1974a: 26: 31–37.

Schmid E., Rimpl G. and Bauchinger M. Dose–response relation of chromosome aberrations in human lymphocytes after *in vitro* irradiation with 3-MeV electrons. *Radiat. Res.* 1974b: 57: 228–238.

Schmid E., Bauchinger M. and Mergenthaler W. Analysis of the time relationship for the interaction of X-ray-induced primary breaks in the formation of dicentric chromosomes. *Int. J. Radiat. Biol.* 1976: 30: 339–346.

Schmid E., Bauchinger M., Streng S. and Nahrstedt U. The effect of 220 kVp X-rays with different spectra on the dose response of chromosome aberrations in human lymphocytes. *Rad. Environ. Biophys.* 1984: 23: 305–309.

Schmitz-Feuerhake I., Schroeder H., Dannheim B., Grell-Buchtmann I., Heimers A., Hoffmann W., Nahrmann A. and Tomalik P. Leukaemia near water nuclear reactor [letter]. *Lancet* 1993: 342: 1484.

Schmitz-Feuerhake I., v. Boetticher H., Dannheim B., Götz K., Grell-Büchtmann I., Heimers A., Hoffmann W., Schröder H., Tomalik P. Rekonstruktion von Strahlenbelastungen bei zwei norddeutschen Leukämieclustern durch Biologische Dosimetrie. In: Koelzer W. and Maushart, R. (Eds.), Strahlenschutz: Physik und Meßtechnik, Band II, 26. Jahrestagung des Fachverbandes für Strahlenschutz Karlsruhe. 1994: pp. 616–621.

Schmitz-Feuerhake I., Dannheim B., Heimers A., Oberheitmann B., Schröder H. and Ziggel H. Leukemia in the proximity of a German boiling-water nuclear reactor: Evidence of population exposure by chromosome studies and environmental radioactivity. *Environ. Health Perspect.* 1996: 105: 1499–1504.

Schwartz G.G. Chromosome aberrations. In: Hulka B.S., Wilcosky T.C. and Griffith J.D. (Eds.), Biological Markers in Epidemiology. Oxford University Press, Oxford, NY. 1990: pp. 147–172.

Scott D. and Lyons C.Y. Homogenous sensitivity of human peripheral blood lymphocytes to radiation-induced chromosome damage. *Nature* 1979: 278: 756–758.

Scott D., Sharpe H.B.A., Batchelor A.L., Evans H.J. and Papworth D.G. Radiation-induced chromosome damage in human peripheral blood lymphocytes *in vitro*: I. RBE and dose-rate studies with fast neutrons. *Mut. Res.* 1969: 8: 367–381.

Scott D., Sharpe H.B.A., Batchelor A.L., Evans H.J. and Papworth D.G. Radiation-induced chromosome damage in human peripheral blood lymphocytes *in vitro*: II. RBE and dose-rate studies with ^{60}Co gamma-and X-rays. *Mut. Res.* 1970: 9: 225–237.

Sharma T. and Das C. The effect of storage of blood on the yield of X-ray-induced chromosome aberrations and spontaneous sister chromatid exchanges. *Int. J. Radiat. Biol.* 1984: 45: 151–158.

Sharma T. and Das B.C. Higher incidence of spontaneous sister-chromatid exchanges (SCEs) and X-ray-induced chromosome aberrations in peripheral blood lymphocytes during pregnancy. *Mut. Res.* 1986: 174: 27–33.

Sharpe H.B.A. Pitfalls in the use of chromosome aberration analysis for biological radiation dosimetry. *Br. J. Radiol.* 1969: 42: 943–944.

Sharpe H.B.A., Scott D. and Dolphin G.W. Chromosome aberrations induced in human lymphocytes by X-irradiation *in vitro*: The effect of culture techniques and blood donors on aberration yield. *Mut. Res.* 1969: 7: 453–461.

Silberstein E.B., Ewing C.J., Bahr G.K. and Kereiakes J.G. The human lymphocyte as a radiobiological dosimeter after total body irradiation. *Radiat. Res.* 1974: 59: 658–664.

Standing Committee on Human Cytogenetic Nomenclature. An international System for human cytogenetic nomenclature (1985) ISCN 1985. S. Karger Medical and Scientific Publishers, Basel, München, London, New York, Tokyo, Sydney, 1985.

Stenstrand K., Annanäki M. and Rytömaa T. Cytogenetic investigation of people in Finland using household water with high natural radioactivity. *Health Phys.* 1979: 36: 441–444.

Stephan G. Biologische Dosimetrie. In: Schütz J. (Ed.), Medizinische Physik. 1983: 319–330.

Stephan G. Körperdosisermittlung durch Chromosomenanalyse. In: Niklas K., Börner W., Holecke F. and Messerschmidt O. (Eds.), Tschernobyl und die Folgen, Begutachtung von Strahlenschäden. Gustav Fischer Verlag, Stuttgart, New York. 1987: pp. 135–148.

Stephan G. and Oestreicher U. An increased frequency of structural chromosome aberrations in persons present in the vicinity of Chernobyl during and after the reactor accident. Is this effect caused by radiation exposure? *Mut. Res.* 1989: 223: 7–12.

Stephan G., Hadnagy W., Hammermaier C. and Imhof U. Biologically and physically recorded doses after an accidental exposure to ^{60}Co-gamma rays. *Health Phys.* 1983: 44: 409–411.

Stevenson A.C., Bedford J., Dolphin G.W., Purrott R.J., Lloyd D.C., Hill A.G.S., Hill H.F.H., Gumpel J.M., Williams D., Scott J.T., Ramsey N.W., Bruckner F.E. and Fearn C.B.D'A. Cytogenetic and scanning study of patients receiving intra-articular injections of gold-198 and yttrium-90. *Ann. Rheum. Dis.* 1973: 32: 112–123.

Stewart J.S.S. and Sanderson A.R. Chromosomal aberration after diagnostic X-irradiation. *Lancet* 1961: 978–979.

Takatsuji T., Takekoshi H. and Sasaki M.S. Induction of chromosome aberrations by 4.9 MeV protons in human lymphocytes. *Int. J. Radiat. Biol.* 1983: 44: 553–562.

Tamura H., Sakurai M. and Sugahara T. A study on time-and radiation-dependent changes in the frequency of lymphocytes with chromosome aberrations in the circulation, following multiple exposures of the pelvis to gamma-irradiation. *Blood* 1970: 36 (1): 43–51.

Tawn E.J. The frequency of chromosome aberrations in a control population. *Mut. Res.* 1987: 182: 303–308.

Todorov S.L. Radiation-induced chromosome aberrations in human peripheral lymphocytes. Exposure to X-rays or protons. *Strahlentherapie* 1975: 149: 197–204.

Tough I.M., Buckton K.E., Baikie A.G. and Court-Brown W.M. X-ray-induced chromosome damage in man. *Lancet* 1960: II: 849–851.

Tucker and Preston, 1996.

UNSCEAR (United Nations Scientific Committee on the Effects of Atomic Radiation). Sources, effects, and risks of ionizing radiation. 1988 Report to the General Assembly. United Nations, New York, 1988.

Urban M., Wicke A. and Kiefer H. Bestimmung der Strahlenbelastung der Bevölkerung durch Radon und dessen kurzlebige Folgeprodukte in Wohnhäusern und im Freien [KFK-Bericht Nr. 3850]. Kernforschungszentrum Karlsruhe (KFK), Eigenverlag, Karlsruhe, 1985.

Veit R., Schmidt B., Pletzer G. and Bauer B. Bestimmung der Strahlenexposition der Bevölkerung durch die Röntgendiagnostik. Teil 2: Ermittlungen zur Dosis. In: Bundesamt für Strahlenschutz (Ed.), Jahresbericht 1992 [ISSN 0940-7650]. BFS, Salzgitter. 1993: pp. 62–64.

Virsik R.P., Harder D. and Hansmann I. The RBE of 30 kV X-Rays for the induction of dicentric chromosomes in human lymphocytes. *Rad. Environ. Biophys.* 1977: 14: 109–121.

Virsik R.P. and Harder D. Recovery kinetics of radiation-induced chromosome aberrations in human Go lymphocytes. *Rad. Environ. Biophys.* 1980: 18: 221–238.

Virsik R.P., Schaefer C., Harder D., Godhead D.T., Cox R. and Thacker J. Chromosome aberrations induced in human lymphocytes by ultrasoft AlK and CK X-rays. *Int. J. Radiat. Biol.* 1980: 38: 545–557.

Virsik-Peuckert R.P. Strahleninduzierte Chromosomenaberrationen in menschlichen Lymphocyten unter dem Einfluß der Strahlenqualität und der zeitlichen Dosisverteilung. Ein Beitrag zur Analyse der Wechselwirkungen strahleninduzierter Primärläsionen des Chromatins (Habilitationsschrift). Medizinische Fakultät der Universität Göttingen, Göttingen, 1981.

Vulpis N. and Coppola M. Ratio of acentrics to dicentrics in human lymphocytes exposed to X rays and misonidazole. *Mut. Res.* 1990: 245: 107–110.

Vulpis N., Tognacci L. and Scarpa G. Chromosome aberrations as a dosimetric technique for fission neutrons over the dose-range 0.2–50 rad. *Int. J. Radiat. Biol.* 1978: 33: 301–306.

Wagner R., Schmid E. and Bauchinger M. Application of conventional and FPG staining for the analysis of chromosome aberrations induced by low levels of dose in human lymphocytes. *Mut. Res.* 1983: 109: 65–71.

Wang Z.Y., Boice J.D. jr, Wei L.X., Beebe G.W., Zha Y.R., Kaplan M.M., Tao Z.F., Maxon H.R. III, Zhang S.Z., Schneider A.B., Tan B., Wesseler T.A., Chen D., Ershow A.G., Kleinerman R.A., Littlefield L.G. and Preston D. Thyroid nodularity and chromosome aberrations among women in areas of high background radiation in China. *JNCI* 1990: 82: 478–485.

Watson G.E. and Gillies N.E. Radiation-induced chromosomal aberrations in human lymphocytes after partial-body exposure to ^{60}Co gamma-irradiation and *in vitro* exposure to 230 kV X-irradiation. *Br. J. Radiol.* 1975: 48: 487–493.

Weber J. Die Abschätzung der Dosis ionisierender Strahlung mit Hilfe der Chromosomenanalyse-Biologische Dosimetrie. In: Köhnlein W., Kuni H. and Schmitz-Feuerhake I. (Eds.), Niedrigdosisstrahlung und Gesundheit. Springer Verlag, Berlin. 1990: pp. 31–41.

Weber J., Scheid W. and Traut H. Biological dosimetry after extensive diagnostic X-ray exposure. *Health Phys.* 1995: 68: 266–269.

White C.M. An experiment to determine the effect of postal delays on aberration yields, Appendix 1. In: The study of chromosome aberration yield in human lymphocytes as an indicator of radiation dose: IV. A review of cases investigated 1973. National Radiation Protection Board (NRPB), Harwell, Didcot, Oxon, UK. 1974: pp. 12–17.

Wolf U., Fender H. and Arndt D. Anwendung ionisierender Strahlung in Ostdeutschland. *Bundesgesundheitsblatt* 1991: 11: 519–524.

Ziemba-Zoltowska B., Bocian E., Rosiek O. and Sablinski J. Chromosome aberrations induced by low doses of X-rays in human lymphocytes *in vitro*. *Int. J. Radiat. Biol.* 1980: 37: 231–236.