Biomonitoring on Carcinogenic Metals and Oxidative DNA Damage in a Cross-Sectional Study


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Abstract

Oxidative DNA damage is mediated by reactive oxygen species and is supposed to play an important role in various diseases including cancer. The endogenous amount of reactive oxygen species may be enhanced by the exposure to genotoxic metals. A cross-sectional study was conducted from 1993 to 1994 in an urban population in Germany to investigate the association between metal exposure and oxidative DNA damage.

The cross-sectional sample of 824 participants was recruited from the registry of residents in Bremen, comprising about two-thirds males and one-third females with an average age of 61.1 years. A standardized questionnaire was used to obtain the occupational and smoking history. The incorporated dose of exposure to metals was assessed by biological monitoring. Chromium, cadmium, and nickel were measured in 593 urine samples. Lead was determined in blood samples of 227 participants. As a biomarker for oxidative DNA damage, 7,8-dihydro-8-oxoguanine has been analyzed in lymphocytes of 201 participants. Oxidative lesions were identified by single strand breaks induced by the bacterial formamidopyrimidine-DNA glycosylase (Fpg) in combination with the alkaline unwinding approach.

The concentrations of metals indicate a low body load (median values: 1.0 µg nickel/l urine, 0.4 µg cadmium/l urine, and 46 µg lead/l blood; 83% of chromium measures were below the technical detection limit of 0.3 µg/l). The median level of Fpg-sensitive DNA lesions was 0.23 lesions/10⁶ bp. A positive association between nickel and the rate of oxidative DNA lesions (Fpg-sensitive sites) was observed (odds ratio, 2.15; tertiles 1 versus 3, P < 0.05), which provides further evidence for the genotoxic effect of nickel in the general population.

Introduction

Pollution of the environment and human exposure to metals occur as a result of natural erosion of metal-containing minerals and as a result of human activities such as mining, smelting, fossil fuel combustion, and industrial application of metals. The highest exposure usually occurs at the workplace. In addition, metal compounds in the general environment can be solubilized in water and become available for uptake by vegetation and consumption by animals. Hence, significant exposure may occur through food, beverages, and drinking water. Air pollution is another common exposure route. For smokers, smoking is the major source of cadmium exposure, because tobacco contains significant amounts of cadmium vaporized by the high temperature of the glow. Metals are accumulated in compartments of the body. Excretion may take years or decades (1, 2).

Metals interfere with many cellular reactions. The carcinogenic potential of cadmium, nickel, and chromium compounds is well-established for humans and experimental animals (3, 4). Regarding lead, the epidemiological data are not conclusive with respect to human carcinogenicity, but carcinogenic and cocarcinogenic effects of lead compounds have been demonstrated in experimental animals (5, 6). However, the molecular interactions leading to tumor formation after exposure to metals are still not well understood. One mechanism proposed frequently is an increase in oxidative DNA lesions attributable to metal exposure, mediated either by an increased generation of highly reactive oxygen species and/or by interference with DNA repair processes (7–10).

Oxidative DNA lesions are supposed to play an important role in various diseases including cancer and premature aging (11–16). Among the diverse oxidative DNA lesions, 8-oxo-Gua³ is one of the most frequent base modifications and has attracted special attention because it is premutagenic, causing G to T transversions. Thus, 8-oxo-Gua is regarded as a suitable biomarker of oxidative stress (16, 17).

The main objective of this study was to quantify the level of oxidative DNA damage in a human study population and to investigate possible associations between the incorporated concentrations of cadmium, chromium, nickel, and lead and the rate of oxidative DNA lesions in lymphocytes. In the present study, we investigated the level of oxidative DNA base modifications in lymphocytes of 201 participants of a cross-sectional study in Bremen, Germany. We applied a method

³ The abbreviations used are: 8-oxo-Gua, 7,8-dihydro-8-oxoguanine; Fpg, formamidopyrimidine-DNA glycosylase; HPLC/ECD, high-performance liquid chromatography/electrochemical detection; GC/MS, gas chromatography/mass spectrometry; OR, odds ratio.
developed recently in our laboratory, which thus far has been used mainly to quantify oxidative DNA lesions in cultured mammalian cells (18).

**Materials and Methods**

**Study Population and Data Collection.** The survey was conducted between 1993 and 1994 with a randomly selected cross-section of inhabitants of Bremen. The study population comprised a total of 824 participants. The sample was drawn from the compulsory municipality registry of residents. All German residents of the city of Bremen in the age range 35–80 years were eligible. The response proportion was 61% for interview (49% interviews conducted, 29% refusals, 3% no contact, 11% not traceable, and 9% too ill for interview). The cross-sectional proportion of the completed case-control study, including 592 men and 232 women. The average age was 61.1 years.

The study participants were interviewed by trained interviewers. A structured questionnaire was used in personal interviews to obtain information on all jobs held after school, smoking history, a food-frequency questionnaire, and basic demographic characteristics. Job-specific supplementary questionnaires were used to obtain detailed information on occupational exposure.

In addition, a medical examination of participants was performed at the study center. The medical examination was offered to participants as a health check-up and comprised the measurement of blood pressure, body height, body weight, and the analysis of blood and urine. From 824 interviewed persons, a total of 62% (n = 516) participated in the medical examination.

The participation in such a health check-up might indicate a higher prevalence of better education, higher socio-economic status, and/or improved health consciousness. To investigate the possibility of a selection bias, smoking status, highest school education, and vocational training were compared between responders and nonresponders to the medical examination. The data do not show substantial differences (Table 1). No statistically significant age difference could be detected (average age of male participants versus nonparticipants, 61.9 years; average age of female participants versus nonparticipants, 59.7 versus 63.7 years).

**Analysis of the Concentrations of Metals in Blood and Urine Samples.** A total of 593 urine samples, most of them morning urine, had been collected during the medical examination in the study center or subsequently at the interview at the participants' home. The collected urine samples were analyzed to assess the concentrations of chromium, cadmium, and nickel. In addition, the concentration of creatinine was measured in urine samples to account for dilution effects. All sampling materials, analytical glass, and plasticware purchased were of low-metal grade.

**Monitoring of Oxidative DNA Damage in Lymphocytes.** Because the laboratory could process only a limited number of specimens each day, blood sample analyses from at most 10 participants equivalent to 40 analytical samples per study day could be carried out. Because of these technical restrictions, the blood samples of 201 participants, who were examined in the morning hours, have been considered for DNA analysis. Blood was drawn by trained personnel into heparinized syringes and stored at room temperature until analyzed. Lymphocytes were isolated within 5 h after blood withdrawal. Samples were analyzed twice, each with and without Fpg incubation. Hence,

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**Table 1** Distribution of smoking, school education, and vocational training for responders and nonresponders of the medical examination

<table>
<thead>
<tr>
<th></th>
<th>Men</th>
<th>Women</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Participation in the medical examination</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>n (%)</td>
<td>(%)</td>
<td></td>
</tr>
<tr>
<td>Smoking status</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nonsmoker or occasional smoker</td>
<td>60 (16.8)</td>
<td>80 (59.7)</td>
</tr>
<tr>
<td>Smoker</td>
<td>297 (83.2)</td>
<td>54 (40.3)</td>
</tr>
<tr>
<td>Highest school education</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Did not complete school</td>
<td>4 (1.1)</td>
<td>2 (1.5)</td>
</tr>
<tr>
<td>Elementary school</td>
<td>217 (60.8)</td>
<td>73 (54.5)</td>
</tr>
<tr>
<td>Middle school (O-level)</td>
<td>74 (20.7)</td>
<td>34 (25.4)</td>
</tr>
<tr>
<td>Technical school</td>
<td>19 (5.3)</td>
<td>4 (3.0)</td>
</tr>
<tr>
<td>High school (A-level)</td>
<td>42 (11.6)</td>
<td>21 (15.7)</td>
</tr>
<tr>
<td>Other school</td>
<td>1 (0.3)</td>
<td>—</td>
</tr>
<tr>
<td>Highest vocational training</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Non</td>
<td>33 (9.2)</td>
<td>42 (31.3)</td>
</tr>
<tr>
<td>Apprenticeship</td>
<td>161 (45.1)</td>
<td>35 (26.1)</td>
</tr>
<tr>
<td>Apprenticeship or commercial</td>
<td>62 (17.4)</td>
<td>33 (24.6)</td>
</tr>
<tr>
<td>Technical school</td>
<td>45 (12.6)</td>
<td>4 (3.0)</td>
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<tr>
<td>Technical college or university</td>
<td>51 (14.3)</td>
<td>18 (13.4)</td>
</tr>
<tr>
<td>Other</td>
<td>5 (1.5)</td>
<td>2 (1.5)</td>
</tr>
<tr>
<td>Total</td>
<td>357 (100)</td>
<td>134 (100)</td>
</tr>
</tbody>
</table>

*Technical, agricultural, or trade.

*Significant (P < 0.05; two-sided χ² test).
allowed to unwind at pH 12.3 for 30 min at room temperature in the dark; the unwinding is stopped by neutralization and sonication. Single- and double-stranded DNA are separated on small hydroxyapatite columns, and the respective amounts are quantified fluorimetrically by the addition of the fluorescence dye Hoechst 33258.

To quantitate the frequency of Fpg-sensitive sites, the fraction of double-stranded DNA was correlated with the amount of DNA strand breaks by calibration with X-rays using a 200 keV X-ray source at a dose-rate of 4 Gy/min with an additional 0.5-mm copper filter (Siemens). Lymphocytes covered with RPMI 1640 were irradiated on ice with different doses of X-rays (0–50 Gy). Subsequently, the lysis and further procedure were carried out as described above, but omitting the Fpg protein. According to Föhe and Dikomey (25), the decrease in double-stranded DNA after irradiation with increasing doses of X-rays is described by the formula 

\[ -\ln(F/F_0) = c \times D, \]

where \( F \) is the fraction of double-stranded DNA of irradiated cells, \( F_0 \) is the fraction of double-stranded DNA of unirradiated control cells, \( c \) represents the slope of the calibration curve, and \( D \) is the dose applied in Gy. \( c \) was determined to be 0.06 on the conditions applied. On the basis of a number of 10^3 DNA strand breaks per Gy and cell (26–28), the number of enzyme-sensitive sites and/or DNA strand breaks per cell induced by the DNA-damaging agents was calculated by the following equation:

\[ N = \frac{-\ln(F/F_0) \times 1000}{c} \]

The whole procedure has been optimized with respect to incubation conditions with the Fpg protein (salt concentration, Fpg concentration, and incubation time, ensuring optimal detection of Fpg-sensitive sites).

**Quality Criteria for the Monitoring of Oxidative DNA Damage in Lymphocytes.** Because the application of this method for lymphocytes was new and had never been applied in an epidemiological study before, double determinations of Fpg-sensitive sites in lymphocytes have been conducted for each participant to obtain a measure of the reproducibility of the test system. Because the analyses have been conducted in groups of 9–11 participants during an entire time period of 2 years and the correct calculation of Fpg-sensitive sites depends on the exact alkaline unwinding conditions on each study day, HeLa cells were analyzed in parallel. HeLa cells should show at least 60% control values for double-stranded DNA. Only lymphocyte samples from those days have been considered for statistical evaluation where HeLa cells exerted control values of 60% and higher. Because of this criterion, 1 set of 10 samples has been excluded. In addition, only those samples were included where both analytical values did not differ by >15%. This rigid quality criterion led to the exclusion of 50 more samples, leaving 141 samples (70.2%) for further statistical calculations.

**Statistical Analysis.** To investigate the relationship between the rate of DNA lesions and incorporated exposure to metals we used both the linear and logistic regression analysis. The model parameter was estimated using the ordinary least-squares criterion. The necessary model assumptions of constancy of error variance and symmetry of distribution of the dependent variable (oxidative DNA lesions) for the linear regression were achieved by a nonlinear Box-Cox transformation (29). This parametric transformation works with two unknown parameters (\( \lambda \) and...
Carcinogenic Metals and Oxidative DNA Damage in Lymphocytes

The shift parameter $\lambda_2$ was a priori defined as the 1% percentile of the untransformed distribution plus 1. The second parameter $\lambda_1$ was estimated by the maximum likelihood method. The proportion of variance of the oxidative DNA lesions that can be explained by the regressor variables (confounder and metal concentration) was determined by the $R^2$ criterion within the linear regression analysis (30).

For the logistic regression analysis, we transformed all values of the oxidative DNA lesions into a binary response (0, low oxidative DNA lesions; 1, high oxidative DNA lesions), using percentiles of the distribution as cutoff points. This was done in different ways, resulting in three different regression models:

- model I, rate of DNA lesions below the median vs. above the median; model II, rate of DNA lesions for tertiles < 1 versus > 3; and model III, rate of DNA lesions for quartiles < 1 versus 4. The odds ratios as well as the model parameters were fitted by the method of maximum likelihood; the corresponding confidence intervals were determined by the profile likelihood function.

- To exclude possible masking effects caused by personal or external factors (confounding), we included in every linear and logistic regression analysis some additional covariables: age, sex, occupational exposure to X-ray exposure, and two correction terms adjusting for external seasonal influences. Ionizing radiation was a priori seen as a potential confounder for oxidative DNA damage. The two correction terms concerning external seasonal influences were not significantly correlated with other covariables or metal concentration and thus included in the regression models. The statistical computer program SAS (31) was used for all calculations.

**Results**

**Incorporated Exposure to Metals of the Study Population.** The cadmium level measured in urine samples shows a median value of 0.40 and 0.50 µg/l and a maximum value of 3.80 and 5.05 µg/l for women and men, respectively (Table 2). Higher cadmium levels are found in males, presumably because of the higher proportion of smokers and exsmokers in male participants (data not shown). Smokers show an average concentration of 0.60 µg/l, whereas nonsmokers excrete 0.40 µg cadmium/l. Volume-related nickel concentrations in urine samples ranged from 0.4 µg/l to 17.05 µg/l with a median of 1.0 µg/l for both sexes. No significant differences related to smoking habits could be detected. Compared with results obtained in an occupation–exposed population, the measured nickel concentration in urine was low (32). The median lead level in whole blood was 46.0 µg/l for both sexes, ranging from 20 to 156 µg/l. About 80% of all chromium measurements are below the detection limit (0.3 µg/l urine).

Table 3 depicts the metal concentrations for the subsample with DNA analysis. No statistically significant differences could be detected compared with the results for the whole study group. According to the threshold limit values (33), only 7% (% (n = 10) of the subsample were at a high-level exposure for at least one of the metals of interest at the time of data collection.

**Level of Fpg-sensitive Sites.** In Fig. 2, the rate of Fpg-sensitive sites is depicted in categories of 1000 lesions/cell. We observed a median level of 1375 lesions/cell or 0.23 lesions/10^6 bp, and only 7% of the subsample at a high-level exposure for at least one of the metals of interest at the time of data collection.

**Determinants for Oxidative DNA Damage.** The data provide no evidence for an association between the level of oxidative DNA lesions (8-oxo-Gua) and age or sex. No association with smoking status or a quantitative dose-response trend for the average amount of cigarettes smoked per day could be detected (data not shown).
Thus, one might explain the even higher background levels observed by conducted for the determination of 8-hydroxyguanine by sensitive sites (34). Furthermore, the derivatization reaction pronounced decrease in levels published during the last years HPLC analysis applied by several groups have led to a pro-

of this point, special precautions during sample preparation for 8-oxo-Gua might be overestimated by both HPLC and GC/MS. There are several indications that the frequency of DNA damage has been published during the last years. When

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Discussion

Level of Fpg-sensitive Lesions in DNA of Human Blood Lymphocytes. The values for Fpg-sensitive sites in the present study range from not detectable to 2.7 lesions/10^6 bp. A wide range of different values for the extent of endogenous oxidative DNA damage has been published during the last years. When comparing the frequencies of Fpg-sensitive sites obtained in the present study with other studies measuring Fpg-sensitive sites in human lymphocytes, they are of the same order of magnitude (Table 5). On the other hand, the values are considerably lower as compared with the amount of 8-oxo-Gua detected by HPLC/ECD or GC/MS (Table 6). This raises the question as to which estimate resembles the “true” frequency of oxidative DNA damage. There are several indications that the frequency of 8-oxo-Gua might be overestimated by both HPLC and GC/MS. Oxidative DNA damage might be introduced unintentionally during the DNA isolation and digestion procedure. In support of this point, special precautions during sample preparation for HPLC analysis applied by several groups have led to a p-

nounced decrease in levels published during the last years (Table 6), reaching values close to the frequency of Fpg-
sensitive sites (34). Furthermore, the derivatization reaction conducted for the determination of 8-hydroxyguanine by GC/MS may lead to an artifactual generation of 8-oxo-G, which might explain the even higher background levels observed by GC/MS as compared with HPLC with ECD (35). Thus, one important advantage of the procedure applied in the present study is certainly the fact that neither isolation of DNA nor derivatization are needed, and only a few minutes are required from cell lysis until incubation with the Fpg protein (for further discussion, see Ref. 24). Therefore, the Fpg-sensitive sites determined in human lymphocytes in this cross-sectional study may provide an important estimate of the level of oxidative DNA damage. Assuming that the steady-state levels of Fpg-sensitive sites resemble realistic approximations of the degree of oxidative DNA damage in human lymphocytes, the test system is very sensitive with respect to small changes in the extent of oxidative DNA damage. Furthermore, the data supply an important basis to identify prooxidative and protective dietary and environmental factors affecting the extent of oxidative DNA damage. Taken together, the assessment of Fpg-sensitive sites may be a valuable biomarker of oxidative stress.

Determinants of Fpg-sensitive Lesions. The data provide no evidence for an association between the level of oxidative DNA lesions and age, sex, or smoking habits. Increased oxidative stress induced by tobacco consumption might enhance the endogenous amount of oxidative DNA damage, but published results are not conclusive (36–38). One could speculate on an association between age and oxidative DNA damage, because of an age-related decline in DNA repair capacity paralleled by cumulation of exposure through occupation or environment. However, our study population comprised only a small age range, which might impair the detection of an association between age and the amount of DNA lesions.

Concentrations of lead in blood or urine samples are determined by current and/or accumulated exposure. Lympho-
cytes are readily accessible, and they can take up reactive intermediates from a variety of body tissues with which they come into contact. In our study, no statistically significant relation was found between the concentrations of cadmium, chromium, lead, and the amount of DNA damage in lymphocytes. The lack of correlation between exposure to cadmium and oxidative DNA damage in lymphocytes could be attributable to a low exposure of the study population. Nonsmoking, non-occupationally-exposed individuals have urine levels be-

between 0.1 and 0.7 μg/l blood.

Although no statistically significant relation was found between the concentrations of cadmium, chromium, lead, and oxidative DNA damage, an association exists between the nickel concentration measured in urine samples (adjusted for creatinine) and the amount of oxidative DNA lesions in lymphocytes (Table 7). This effect is confirmed by the logistic regression analysis (Table 8). The increasing ORs from model 1 to model 3 suggest a dose-response relationship between the nickel concentration and frequency of oxidative DNA lesions. If those 60 samples were included in the statistical analyses that were excluded because of the quality criteria (tertiles 1 to model 3; OR, 1.74; confidence limits, 1.0–2.66) the conclusions of the study would not change substantially.

### Table 3 Concentrations of metals in participants with DNA measurements

<table>
<thead>
<tr>
<th></th>
<th>Men</th>
<th>Women</th>
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<th>Women</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cadmium (μg/l urine)</td>
<td>98</td>
<td>40</td>
<td>3.15</td>
<td>2.40</td>
</tr>
<tr>
<td>Cadmium (μg/g urinary creatinine)</td>
<td>98</td>
<td>40</td>
<td>1.76</td>
<td>1.38</td>
</tr>
<tr>
<td>Nickel (μg/l urine)</td>
<td>100</td>
<td>40</td>
<td>7.0</td>
<td>4.50</td>
</tr>
<tr>
<td>Lead (μg/l blood)</td>
<td>100</td>
<td>39</td>
<td>156.0</td>
<td>90.0</td>
</tr>
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</table>

a Detection limit, 0.2 μg/l urine.

b Detection limit, 0.1 μg/l urine.

c Detection limit, 20 μg/l blood.

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<th>90% percentile</th>
<th>Maximum</th>
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<tr>
<td>Cadmium (μg/l urine)</td>
<td>98</td>
<td>0.44</td>
<td>0.50</td>
<td>1.1</td>
<td>3.15</td>
</tr>
<tr>
<td>Cadmium (μg/g urinary creatinine)</td>
<td>40</td>
<td>0.33</td>
<td>0.40</td>
<td>0.75</td>
<td>2.40</td>
</tr>
<tr>
<td>Nickel (μg/l urine)</td>
<td>100</td>
<td>0.84</td>
<td>1.00</td>
<td>2.35</td>
<td>7.0</td>
</tr>
<tr>
<td>Lead (μg/l blood)</td>
<td>100</td>
<td>48.6</td>
<td>47.5</td>
<td>79.0</td>
<td>156.0</td>
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The data provide no evidence for an association between the level of oxidative DNA lesions and age, sex, or smoking habits. Increased oxidative stress induced by tobacco consumption might enhance the endogenous amount of oxidative DNA damage, but published results are not conclusive (36–38). One could speculate on an association between age and oxidative DNA damage, because of an age-related decline in DNA repair capacity paralleled by cumulation of exposure through occupation or environment. However, our study population comprised only a small age range, which might impair the detection of an association between age and the amount of DNA lesions.

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Nickel is used in the production of stainless steel, high-nickel alloys, Ni-Cd batteries, and electronic components. A major fraction of nickel absorbed by humans appears to be eliminated relatively quickly, mainly via urine. The biological half-life has been estimated to be between 1 and 2 days. Moderately increased concentrations of nickel have been found in the urine and blood of workers exposed to nickel, even after exposure has long been ceased. Thus, a small fraction of absorbed nickel will accumulate in the body and will be eliminated only slowly (1). The positive association between nickel content in urine and DNA lesions in lymphocytes provides further evidence for the genotoxic effects of this metal. The carcinogenicity of nickel has been established. An increased risk for lung cancer has been reported attributable to occupational exposure to nickel compounds (1). The evidence from human and experimental studies indicates that exposure via the respiratory route to soluble compounds of nickel results in respiratory cancer (2). Nickel has been shown to inhibit the repair of oxidative DNA lesions (9). A reduced repair capacity of oxidative DNA damage might enhance the level of the studied lesions in vivo and hence might increase the risk of developing cancer. Because the repair of DNA damage is essential for the prevention of cancers, the inhibition may account for the carcinogenic action of nickel.

However, it should be considered that there might be some uncertainties regarding the assessment of the exposure to nickel and the assessment of the related biological effect. Knowledge of the kinetics of the measured substance in the central plasma compartment, in the elimination compartments, especially
urine, and in storage compartments is essential to establish the correct organ site and time for sampling and the number of samples that should be taken. Another critical issue is the persistence of the biological effects of carcinogens in target tissues. Lymphocytes are used frequently for the measurement of oxidative DNA modifications, because they can themselves be possible target cells for carcinogenic agents. Because the lifespan of different lymphocyte subpopulations may vary from a few days to several years and the size of these populations can be influenced by a variety of immunological stimuli, the persistence of DNA lesions in lymphocytes cannot be estimated in general. For future directions, a longitudinal rather than a cross-sectional study should be conducted to ascertain the possible association between nickel exposure and oxidative DNA lesions. A longitudinal study that includes a relevant number of occupationally exposed participants offers an advantage for studying dose–effect relationships over time with repeated measurements.

Acknowledgments
We thank Dr. J. Dahm-Daphi, Hamburg, Germany, for help in calibrating the alkaline unwinding technique with X-rays. The Fpg protein was a kind gift of Dr. Serge Boiteux, Fontany aux Roses, France. We also thank Ines Pelz for excellent management of the data collection.

References


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