

Occupational Exposure to Lead and Induction of Genetic Damage

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To investigate whether occupational exposure to lead is genotoxic, we evaluated data from 103 lead-exposed workers and 78 matched controls. These data correspond to three different sampling periods, and we measured genetic damage as increases in the frequency of binucleated cells with micronuclei (BNMN) in peripheral blood lymphocytes. The levels of exposure were determined according to the lead levels in blood. Clearly significant increases in BNMN were observed in the exposed groups when compared to the control group. In addition, for the overall population ($n = 181$), we observed a clear relationship between lead levels in blood and BNMN ($r = 0.497$; $p < 0.001$). When we examined four exposure levels—very low exposure ($< 1.20 \mu\text{M/L}$), low exposure ($1.20\text{--}1.91 \mu\text{M/L}$), high exposure ($1.92\text{--}2.88 \mu\text{M/L}$), and very high exposure ($> 2.88 \mu\text{M/L}$)—we found significant differences in the genetic damage induction. We conclude that exposure to levels of lead higher than $1.20 \mu\text{M/L}$ may pose an increase in genetic risk. In addition, our data show that blood lead level is a good indicator of genetic damage induction. **Key words:** biomonitoring, genotoxicity, lead-exposed workers, lymphocytes, micronucleus assay. *Environ Health Perspect* 109:295–298 (2001). [Online 5 March 2001]

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Lead (Pb), a toxic contaminant metal used in many important industrial processes, is widely used in batteries, paint, and varnishes, as an antiknock compound in gasoline, in pipe covering, and in welding. Because of its persistence in the environment, exposure to lead has become a major public health concern. Chronic, low-level exposure to lead affects children living in old homes and/or children in families with low income (1), as well as other groups that are occupationally exposed to high lead levels. The study of these highly exposed persons provides the opportunity to establish relationships between exposure levels and different toxic end points.

Although lead toxicity on different biological systems and functions has been well reported (2–4), there are conflicting data on its genotoxic and carcinogenic properties. In bacterial tests, lead seems to be generally nonmutagenic (5). Nevertheless, in eukaryotic cells this metal is usually genotoxic (6,7), through a mechanism that until now has not been well characterized and that possibly involves indirect damage to DNA, affecting the stabilization of chromatin (8) or interacting with repair processes (9).

Whether lead is carcinogenic to humans is still not known. The International Agency for Research on Cancer (IARC) classified lead and inorganic lead compounds as possible human carcinogens (Group 2B) on the basis of sufficient evidence for carcinogenicity in experimental animals but inadequate evidence for carcinogenicity in humans (10). A quantitative assessment of published data, with workers heavily exposed to inorganic lead, provides some evidence to support the

hypothesis of an association between stomach and lung cancer and exposure to lead (11), but this meta-analysis is limited significantly by the lack of information about potential confounding factors.

To learn more about the possible relationship between lead exposure and genetic risk, we investigated genetic damage observed in a large group of Bulgarian workers exposed to lead. The data were collected in three periods (1992, 1993, and 1996) and the frequency of micronuclei (MN) was the genetic end point evaluated. MN is considered a reliable biomarker of genotoxic exposure to both physical and chemical agents (12), and increases in MN frequency indicate exposure to clastogenic and/or aneugenic agents. In addition, cytogenetic end points in peripheral blood lymphocytes have been used as biomarkers for many years and allow a reasonable epidemiological evaluation of cancer predictivity (13).

Materials and Methods

Studied populations. Three independent biomonitoring studies were conducted in the years 1992, 1993, and 1996, examining the genotoxic effects of lead exposure in a group of workers from a Bulgarian storage battery plant. The studies assessed cumulative exposures by monitoring concentrations of lead in blood and by cytogenetic monitoring with the micronucleus assay in peripheral blood lymphocytes. We sampled 181 men in three sessions. The first sample included 16 controls and 29 exposed, the second included 24 controls and 49 exposed, and the third, 38 controls and 25 exposed. The 103 workers exposed to lead participating in the study

were employed in a storage battery plant located in Pazardzik, Bulgaria. These men were constantly exposed at their workplaces to lead concentrations in air 2–15 times the permissible exposure limit (0.05 mg/m^3 ; PEL). The control group of 78 males was divided in two subgroups as follows: an internal control group of 43 persons from the administrative and maintenance staff from the same plant and an external control group of 35 persons recruited from a non-contaminated plant in the same town.

The questionnaire and clinical examination of all the individuals studied were performed the same day as blood sampling by occupational expert pathologists to select the appropriate subjects for the study. Individuals exposed to other genotoxic agents were not included in the study, and the exposed and control individuals were matched for relevant factors such as age, smoking, and drinking habits. Each donor gave written consent before the investigations, and blood samples were collected and manipulated in accordance with ethical standards.

The lead concentrations in the blood of each participant were determined by using an AAS PerkinElmer 3030 device (PerkinElmer, Norwalk, CT, USA) after flame extraction the day after sampling.

Cell cultures and MN analysis. Blood samples were obtained by venipuncture in heparinized sterile tubes, coded, and sent immediately to the laboratory where they were processed. Lymphocyte cultures were started by adding 0.5 mL of blood to 5 mL RPMI-1640 medium (Sigma, St. Louis,

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MO, USA), supplemented with phytohemagglutinin (PHA; Gibco, Grand Island, NY, USA), 15% fetal calf serum (Sigma), and 1% penicillin and streptomycin.

The cultures were incubated at 37°C and 5% CO₂ for 72 hr. Cytokinesis was blocked with 6 µg/mL cytochalasin B (Sigma) added 44 hr after PHA stimulation. Cells were harvested by centrifugation and, after a mild hypotonic treatment with 3 mL 0.075 M KCl at 4°C and another centrifugation, were fixed by adding 5 mL fixative solution (methanol:glacial acetic acid, 3:1). Then 50 µL formaldehyde were added during the next hour. We next performed two steps of centrifugation, with consequent fixation of the material as already described, without adding any more formaldehyde. Air-dried preparations were stained with 5% Giemsa (Merck, Darmstadt, Germany) for 15 min. MN were scored in 1,000 binucleated lymphocytes per donor according to Fenech (12).

To minimize variability, the same experts performed all the microscopic analyses during the study. All scoring was performed blind, with no knowledge of the samples origin.

Statistical methods. For the investigations done in 1992, 1993, and 1996, we compared the distribution of BNMN and the distribution of blood lead concentration with the normal distribution by means of the Kolmogorov-Smirnov test of goodness of fit. Neither distribution departed significantly from normality and therefore parametric tests were adequate for the statistical analysis. For each independent study, the effects of some factors on binucleated micronuclei (BNMN) were simultaneously assessed by analysis of variance (ANOVA). These factors were occupational exposure, smoking habits, and alcohol consumption, with age of the subject considered as a covariate. To determine the relationship between lead exposure levels and BNMN, we applied a multiple regression analysis to the whole investigated population. This analysis was carried out by using the CSS:STATISTIC/W (StatSoft, Tulsa, OK, USA) statistical package.

Results

Tables 1 and 2 show the characteristics of the control and exposed groups, respectively. Age of individuals, years in their employment, and smoking and drinking habits are indicated. Lead levels in blood are also shown. These results are presented for each sampling period as well as for the pooled data. Lead in blood for the exposed workers was about three times higher than the values obtained for the controls, indicating that the exposure levels were high.

Table 3 shows the results of the MN scoring, indicating both the average total number of MN scored for 1,000 binucleated cells, as well as the average of binucleated cells presenting one or more MN. This second measurement has been considered a good parameter for measuring genotoxic effects (14). The overall frequency of BNMN in the pooled control was 20.24 ± 1.02, which is in good agreement with values usually reported for control populations.

When we compared BNMN from sampling periods for controls, we found no differences between 1992 and 1993 ($p = 0.67$), 1992 and 1996 ($p = 0.32$), or 1993 and 1996 ($p = 0.52$). Furthermore, when all the controls were grouped as internal controls ($n = 43$) and external controls ($n = 35$), the statistical analysis showed that the differences were not statistically significant ($p = 0.18$). Thus, the pooled data can be considered as a good reference control.

When the overall control data for BNMN were compared with the pooled exposed data, the differences were significant ($p < 0.001$), indicating a clear genotoxic effect of lead exposure. Figure 1 shows the values of the exposed group compared with both the internal and external control groups. These differences between exposed and controls were also observed for each of the sampling periods ($p < 0.001$; $p = 0.0017$; and $p < 0.001$ for 1992, 1993, and 1996, respectively).

The genetic effects detected in the exposed group are considered to be caused by lead exposure. The average values of lead in blood for the exposed and for the internal and external controls are indicated in Figure 2. This figure demonstrates that, despite the lack of significance for the BNMN values between internal and external controls, the values of lead in blood are higher in the internal control ($p = 0.000198$). Nevertheless, both control values are significantly lower than values observed in the exposed group ($p < 0.001$). The multiple regression analysis indicated a slight relationship between alcohol consumption and BNMN ($p = 0.052$).

Figure 3 shows the relationship between the levels of lead in blood and genotoxic effects, as reflected by the BNMN values. This figure provides data for both the control and the exposed individuals ($n = 181$). A significant correlation ($r = 0.49669$; $p < 0.001$) was found between BNMN and lead in blood, indicating a direct relationship between lead levels in blood and genetic damage induction.

To visualize better the relationship between lead in blood (as a measurement of exposure) and the frequency of BNMN (as a measurement of genetic damage), we categorized the donors in four groups, according to their blood lead levels. These values are indicated in Figure 4, where the four groups, corresponding to very low exposure (< 1.20

Table 1. Characteristics of the three control groups, with lead levels in blood (mean ± SE).

Year	No. of individuals	Age (years)	Years employed	Smoking (cigarettes/day)	Alcohol (g/day)	Pb in blood (µM/L)
1992	16	43.81 ± 2.83	17.51 ± 2.76	10.00 ± 2.41	16.81 ± 3.99	0.52 ± 0.04
1993	24	40.42 ± 1.86	13.33 ± 1.87	9.58 ± 2.13	5.33 ± 2.48	0.87 ± 0.08
1996	38	42.34 ± 1.38	16.71 ± 1.38	12.89 ± 2.02	7.58 ± 2.81	1.11 ± 0.06
Total	78	42.05 ± 1.05	15.83 ± 1.06	11.28 ± 1.28	8.78 ± 1.81	0.91 ± 0.04

Table 2. Characteristics of the three exposed groups, with lead levels in blood (mean ± SE).

Year	No. of individuals	Age (years)	Years employed	Smoking (cigarettes/day)	Alcohol (g/day)	Pb in blood (µM/L)
1992	29	39.72 ± 1.56	11.09 ± 1.25	7.24 ± 1.76	13.24 ± 4.63	2.44 ± 0.21
1993	49	39.26 ± 1.28	8.83 ± 0.85	11.22 ± 1.26	13.71 ± 2.47	2.89 ± 0.14
1996	25	38.24 ± 2.03	9.72 ± 0.96	14.60 ± 1.98	14.08 ± 4.16	2.61 ± 0.16
Total	103	39.14 ± 0.89	9.68 ± 0.59	10.92 ± 0.94	13.67 ± 2.00	2.70 ± 0.10

Table 3. Mean number (± SE) of micronuclei (MN) in binucleated cells and binucleated cells presenting one or more micronuclei (BNMN).

Group	Year	No. of individuals	MN	BNMN
Control	1992	16	19.68 ± 1.98	18.56 ± 1.78
	1993	24	21.04 ± 1.95	19.71 ± 1.81
	1996	38	23.08 ± 1.79	21.29 ± 1.60
	Total	78	21.76 ± 1.13	20.24 ± 1.02
Exposed	1992	29	39.28 ± 2.36	34.59 ± 2.31
	1993	49	35.47 ± 2.59	31.31 ± 2.32
	1996	25	60.80 ± 3.65	52.32 ± 2.89
	Total	103	42.69 ± 1.94	37.33 ± 1.68

We scored 1,000 binucleated cells per donor.

$\mu\text{M/L}$), moderate exposure (1.20–1.91 $\mu\text{M/L}$), high exposure (1.92–2.88 $\mu\text{M/L}$), and very high exposure (> 2.88 $\mu\text{M/L}$), are shown. The number of donors in each group was 71, 32, 29, and 49, respectively. As can be seen, BNMN correlate well with blood lead levels, obtaining significant differences between very low and moderate exposure levels ($p = 0.05$) and moderate and high exposure levels ($p = 0.02$), although not between the high exposure and the very high exposure levels ($p = 0.16$).

Discussion

The workers occupationally exposed to lead who were monitored in this investigation showed clear evidence of genetic damage in peripheral blood lymphocytes when evaluated by using the MN assay. These results extend and confirm our recent studies performed in another group of Bulgarian workers exposed to lead (15) with no apparent exposure to other suspicious genotoxic agents at the workplace.

Once the hazardous workplace or exposures are identified, the major objectives are to establish the relationship between exposure levels and genetic risk and to define safe levels of exposure on a sound toxicological basis. In this context, biomonitoring exposed individuals is extremely important, especially in evaluating genotoxic effects, as

in this study. At present, large follow-up studies suggest that increases in chromosome alterations may predict an increased cancer risk (13,16).

Among the different cytogenetic approaches, the MN assay in human lymphocytes using the cytokinesis-block method (17) has increasingly been accepted as a reliable biomarker of cytogenetic damage induced by genotoxic agents, both physical and chemical (12,18). Positive findings using this biomarker indicate evidence of exposure to clastogenic and/or aneugenic compounds. In particular, the MN assay has proved very reliable in assessing the genotoxic effects of metal ions in occupational exposures (15,19,20).

Regarding the carcinogenic risk of lead exposure, several experiments in rats and mice showed the production of renal tumors when lead compounds were administered in food and drinking water (21). In humans, several epidemiological studies of workers exposed to lead in various occupational settings have been reported. Unfortunately, most of these studies contain some deficiencies, particularly a lack of information about cumulative past exposures, and the overall studies do not provide conclusive evidence of an association between lead exposure and increased incidence of cancer (10,21). Accordingly, lead has been classified by

IARC as a possible human carcinogen on the basis of sufficient evidence in rodents but inadequate evidence in humans (10). Nevertheless, a meta-analysis of published data from workers highly exposed to lead seems to support the hypothesis of an association between exposure to lead and stomach and lung cancer (11).

The relationship that exists between the genotoxic and carcinogenic potential of lead has been the subject of extensive studies, although in most of them the results obtained were inconclusive. Thus, although lead seemed to be negative in an assay detecting mutation induction in bacteria (22), positive results were obtained in an assay detecting induction of λ prophage in *E. coli* (23). In mammalian cells, induction of mutation has been reported in the *hprt* locus in Chinese hamster V79 cells by lead compounds (6), although studies on the induction of chromosomal aberrations, both *in vivo* and *in vitro*, showed ambiguous results because the genotoxic response appears to depend on factors such as cell type, duration, and route of exposure and can also be influenced by synergistic effects. Thus, for instance, calcium-deficient animals exposed to lead demonstrated more severe chromosomal aberrations than nondeficient animals (24). All these variables contribute to the high variability in results.

With respect to the biomonitoring studies performed in humans occupationally exposed to lead, although relatively few studies have examined the genotoxic potential of lead and they offer some equivocal results, most show increases in chromosomal aberrations (25–29). The high degree of variability in the available data represents, perhaps, different levels of exposure and makes the explanation of biomonitoring results quite complex.

In view of the current inconclusive evidence of a direct relationship between *in vivo* lead exposure and induction of genetic damage, we think that the positive findings presented here are satisfactory evidence of a genetic risk associated with lead exposure. It must be remembered that the MN assay detects both clastogenic and aneugenic effects, covering a wider spectrum of damage than the classical chromosome aberrations test. Thus, it could be possible that lead induces genotoxicity via induction of chromosome loss, which would be interesting to confirm.

Although the qualitative data obtained are important, indicating a genetic risk associated with lead exposure, more interesting is the quantitative association found between blood lead levels (as a measurement of exposure) and BNMN (as a measurement of genetic damage). The levels of genotoxins in the body fluids can be regarded as a measure

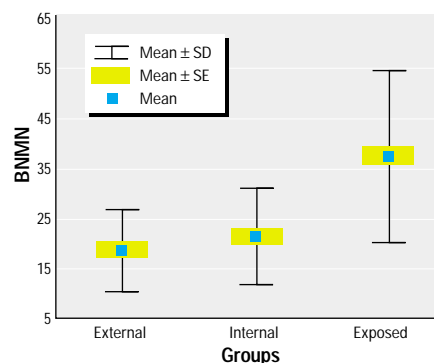


Figure 1. BNMN values obtained for exposed and controls (internal and external).

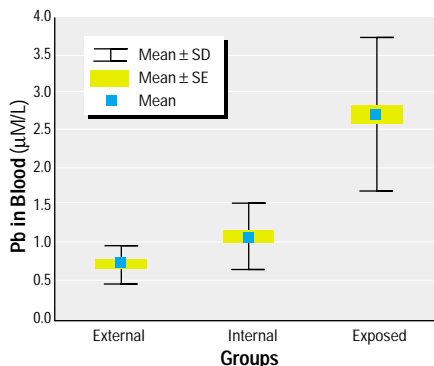


Figure 2. Lead levels in blood from exposed and controls (internal and external).

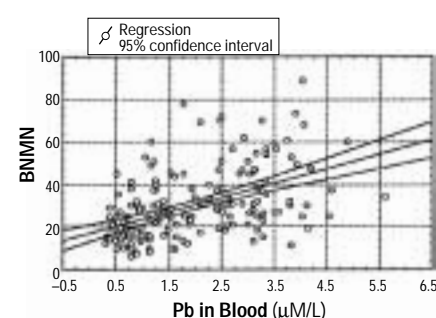


Figure 3. Lead in blood and BNMN relationship in the overall population. $\text{BNMN} = 16.755 + 6.828$ (blood lead); $r = 0.49669$.

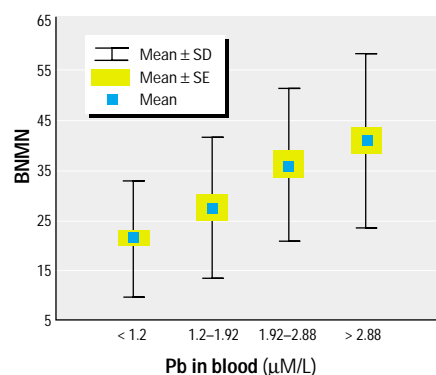


Figure 4. Lead in blood and BNMN relationship for four blood lead levels.

of the internal dose, confirming that exposure has indeed occurred. Cytogenetic alterations as measured by the MN assay are early biological effects in carcinogenesis, if we assume that lymphocytes are valid surrogate cells for the changes taking place in tissues where neoplasms may eventually develop. Nevertheless, the relationship between exposure markers and genetic changes such as chromosome alterations are not always clear (30), depending on the toxicokinetics and distribution of the compound or its metabolites in the body compartments.

In our study, the large sample size and the wide variability found in the blood lead levels made it possible to obtain a good relationship between the exposure and the biomarkers. This allowed us to identify exposure levels as low as 1.20–1.91 $\mu\text{M/L}$, which are associated with significant increases of genetic damage at levels where no clinical symptoms are observed. These lead levels are found in the range reported for different populations not specifically exposed to lead at their workplace (31) and exceed the biological tolerance value regulated in many countries, (e.g., in Germany this value is 3.38 $\mu\text{M/L}$) (32).

In summary, this study shows a clear genotoxic effect associated with the occupational exposure to lead, indicating that this effect is dose-related to the lead levels in blood. These data are relevant and permit an estimate of the genetic risk of lead exposure by using biomarkers of exposure.

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