Biological Monitoring of Workers Exposed to Emissions from Petroleum Plants

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This paper presents some of the results from the Commission of the European Communities collaborative research program (contract number EV5V-CT92-0221), whose aim is to investigate the relationship between exposure to petroleum emissions, benzene, and induction of genetic damage in human cells. Twenty-four workers from petroleum plants in Poland and 35 unexposed controls were examined for cytogenetic effects and ras oncogene levels and their relationship to confounding factors (e.g., smoking habit, sex, family cancer history, and seasonal influence). Preliminary data of chromosome aberrations (CA) and sister chromatid exchanges (SCE) showed differences among sampling subgroups. In this present study, the levels of ras p21 proteins were determined and further analyses of CA, SCE, high frequency cells (HFC), and proliferative rate index (PRI) have been undertaken. Results show that the exposed group has statistically significant increases in CA, and percent of aberrant cells. There were no differences between exposed and unexposed groups in SCE, HFC, PRI, or the levels of ras p21 proteins. Smoking was found to statistically significantly affect levels of CA, percent of aberrant cells, SCE, HFC, and ras proteins. Sister chromatid exchanges were also statistically significantly sex dependent (7.5 breaks/cell for females and 6.8 breaks/cell for males). There were no statistically significant differences for CA, percent aberrant cells, SCE, HFC, or ras p21 protein levels in subgroups characterized according to cancer cases reported in the immediate family. A seasonal variability was shown with statistically significant increases in various biomarkers in the winter. Unexposed groups also showed increases due to smoking and season. The nonsmoking group individuals also showed statistically significant increases in cytogenetic damage with exposure. — Environ Health Perspect 104(Suppl 3):609–613 (1996)

Key words: petroleum emissions, workers, chromosome aberrations, ras oncogenes

Introduction

Chemical carcinogens have the ability to initiate the carcinogenic process by mutagenic or genotoxic mechanisms (1). Benzene is considered to be a human carcinogen, it is clastogenic to rodents and humans, and it affects the immune response (2). Workers in various industrial plants, particularly those in petroleum plants, are exposed to benzene and benzene-related compounds as a result of various activities in which benzene is processed, generated, or used. A Commission of the European Communities collaborative research program (coordinated by Angelo Carere) has been set up to investigate different aspects of the toxicity of benzene. The goals of the program are to describe the exposure profile of human populations occupationally exposed to benzene and petroleum fuels, to analyze the frequency of early indicators of genetic damage in relation to the exposure to the petroleum products, to evaluate the role of benzene as a genotoxic component of petroleum and its derivatives, and to analyze the mortality of filling station attendants in relation to the adversity of exposure to petroleum fuels.

The present study was part of this collaborative program; the aim of this study was to examine cytogenetic effects and ras oncogene levels and their relationship to confounding factors (e.g., smoking habits, sex, family cancer history, and seasonal influences) in samples of peripheral blood lymphocytes and plasma of workers from petroleum plants in Poland by comparison with unexposed controls.

Materials and Methods

Sampling

Interviews were performed using a questionnaire recommended for this type of study (3). Blood samples were collected from several exposed and unexposed subgroups. To avoid a seasonal influence, sampling of exposed and unexposed subgroups was carried out during the same time period either in winter or in summer. Table 1 presents the characteristics of the exposed and unexposed subgroups.

Blood samples from the exposed groups were collected in 1993 and 1994 in two petroleum plants described elsewhere (4,5). The available information on the production and emission of these plants is shown in Table 2. Individual monitoring of workers was not undertaken at the time. Two subgroups of unexposed donors were chosen from administrative staff at the petroleum plant and from the region of southern Poland characterized by a low level of pollution (6) and a low level of total cancer cases (7). Blood samples were collected by venipuncture into heparinized tubes. Each sample was split into two parts. From the first part of the sample, blood plasma was extracted, frozen at −70°C, and transported in dry ice to BIBRA International laboratory for testing ras p21 protein levels by methods discussed.

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Abbreviations used: Abf, aberration frequencies excluding gaps; AbC, percent of aberrant cells; CA, chromosome aberrations; HFC, high frequency cells; PRI, proliferative rate index; ras, ras p21 protein; SCE, sister chromatid exchanges; TABF, total aberration frequencies including gaps.

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Table 1. Characteristics of exposed and unexposed subgroups.

| Exposure | Sampling season | Number of individuals investigated | Age | Female, % | Male, % | Smoking individuals, % | Individuals reporting cancer in family, % | Number of first mitoses analyzed for CA | Number of second mitoses analyzed for SCE |
|----------|----------------|-----------------------------------|-----|-----------|---------|------------------------|------------------------------------------|------------------------------------------|------------------------------------------|
| Exposed  | Winter         | 10                                | 42  | 20        | 80      | 90                     | 20                                       | 2445                                     | 590                                      |
| Exposed  | Summer         | 14                                | 41  | 21        | 79      | 93                     | 0                                        | 1845                                     | 697                                      |
| Total    |                | 24                                | 41  | 21        | 79      | 91                     | 12                                       | 4290                                     | 1287                                     |
| Unexposed| Winter         | 10                                | 40  | 70        | 30      | 60                     | 20                                       | 3232                                     | 742                                      |
| Unexposed| Summer         | 25                                | 39  | 39        | 61      | 67                     | 17                                       | 4476                                     | 1390                                     |
| Total    |                | 35                                | 40  | 50        | 50      | 64                     | 18                                       | 7729                                     | 2132                                     |

Abbreviations: CA, chromosome aberration; SCE, sister chromatid exchanges.

Table 2. The production and emission of the two Polish petroleum plants where blood samples from the exposed groups were collected (1992 figures).

| Production and emission | Central Poland | Southern Poland |
|-------------------------|----------------|-----------------|
| Oil transferred         | 10,000,000     | 135,434         |
| Emission                |                |                 |
| Sulphur dioxide         | 48,113         | 310             |
| Carbon monoxide         | 7,354          | 31              |
| Nitrous oxide           | 5,867          | 183             |
| Hydrogen sulfide        | 65             | 53              |
| Benzene                 | 0.048          |                 |
| Aromatic hydrocarbons   | 784            | 5.2             |
| Aliphatic hydrocarbons  | 6,172          | 231.7           |
| Benzo[a]pyrene          | 0.002          | 0.004           |
| Gaseous in total        | 7              | 782             |
| Dust in total           | 411            | 286             |

Mg, megagram = 1,000 kg or 1 metric ton; ?, unknown.

elsewhere (8,9). The second part of the heparinized whole blood was transported to the laboratory of the Environmental and Radiation Biology Department in Kraków where appropriate culturing of samples was performed as soon as possible.

Blood Culturing and Cytogenetic Screening

Samples of heparinized blood were incubated at 37°C using Eagle’s medium supplemented with 20% fetal calf serum and antibiotics. Lymphocytes were stimulated with LF-7, a Polish substitute for phytohemagglutinin (4,10), and then cultured, with the addition an appropriate amount of 5-bromo-2-deoxyuridine (BrdU) in chromosome aberration (CA) cultures for 48 hr and in sister chromatid exchange (SCE) cultures for 72 hr (11). Ninety minutes before the end of culture, colcemid was added (0.1 µl/ml) to each sample. Fixation and staining were performed by standard cytological procedures for both methods respectively (3,12,13). The number of cells analyzed in the first mitosis for CA and in the second mitosis for SCE are displayed in Table 1. Chromosome- and chromatid-type aberrations were scored and expressed as total aberration frequencies including gaps (TABF) and excluding gaps (AbF). SCEs were screened for each metaphase containing at least 44 chromosomes, and high frequency cells (HFC) were evaluated as reported elsewhere (14,15).

Statistics

A t-test and analysis of variance (ANOVA) were applied to determine whether there was a significant difference between one or more confounding factors and different variables. A significance level lower than 0.05 is reported as *, and a level lower than 0.005 is reported as ** (16).

Results

Table 3 and Figure 1 show yields of various biomarkers detected in blood samples of the entire population under study and their relationship to exposure. In the exposed group there was a statistically significant increase in CA (TABF, AbF, and AbC [percent of aberrant cells]). There was an increase in the level of observed cytogenetic damage that varied significantly with the duration of occupational exposure, but the relationship was

Figure 1. Influence of exposure to benzene-related compounds on biomarkers in the study population. Abbreviations: TABF, total aberration frequency; AbC, percent of aberrant cells; SCE, sister chromatid exchange; HFC, percent of cells containing high frequency SCE; RAS, p21 protein level. **Significance level <0.005.

Table 3. The effect of exposure on various biomarkers in the study population.

| Exposure | Number of individuals in group | Age | TABF ± SE | AbF | AbC | SCE | PRI | HFC | RAS |
|----------|--------------------------------|-----|-----------|-----|-----|-----|-----|-----|-----|
| Whole population under study | 49 | 41 | 0.044 ± 0.014 | 0.30 | 4.1 | 7.1 | 2.35 | 6.3 | 0.84 |
| Unexposed | 25 | 40 | 0.032 ± 0.009** | 0.017** | 3.1** | 6.8 | 2.34 | 6.7 | 0.92 |
| Exposed | 24 | 41 | 0.056 ± 0.018 | 0.043 | 5.3 | 7.2 | 2.28 | 7.0 | 0.74 |
| Years of exposure | | | | | | | | | |
| 0 years | 25 | 40 | 0.032 ± 0.009** | 0.017** | 3.1** | 6.9 | 2.34 | 6.7 | 0.82** |
| < 10 years | 8 | 31 | 0.081 ± 0.026 | 0.069 | 7.3 | 7.0 | 2.36 | 6.3 | 0.96 |
| < 20 years | 14 | 41 | 0.043 ± 0.015 | 0.032 | 4.1 | 7.6 | 2.26 | 7.3 | 1.22 |
| > 20 years | 2 | 43 | 0.053 ± 0.016 | 0.039 | 5.1 | 6.5 | 2.22 | 2.0 | 0.39 |

Abbreviations: TABF ± SE, total aberration frequency (including gaps) ± standard error; AbF, aberration frequency (excluding gaps); AbC, percent of aberrant cells; SCE, sister chromatid exchange; HFC, percent of cells containing high frequency SCE, i.e., containing number of exchanges above 95% of total in control distribution; PRI, proliferative rate index ([MI + 2xMII + 3xMIII] / [MI + MII + MIII]); RAS, p21 protein level. **Significance level <0.005.
not linear (Figure 2). SCE levels were slightly higher in the exposed group but were not statistically significant by comparison with the unexposed group. There were also no significant differences between exposed and unexposed groups in HFC, proliferative rate index (PRI), or the levels of ras p21 proteins (Figure 1). The level of ras p21 showed significant variation with the duration of exposure, but there was no linear correlation between oncoprotein levels and years of occupational exposure (Figure 2).

Results of the analysis regarding confounding factors are presented in Table 4, where smoking was found to cause significant increases in TabF, AbF, AbC, SCE, HFC, and ras (Figure 3). SCE, HFC and ras protein levels showed significant variation with the different categories of smoking habits; however, there was no simple relationship observed between the length or extent of smoking and the level of damage observed (Figure 4). SCEs and HFC were found to be significantly sex (female) dependent (Figure 5). There were no significant differences for CA, SCE, HFC, or ras p21 protein levels in subgroups characterized according to cancer history, i.e., cancer cases reported in the immediate family (Table 4). There were large differences for all the biomarkers in the study in relation to the sampling season (Figure 6). There were statistically significant increases in TabF, AbF, AbC, SCE, and HFC and a decrease in ras p21 when the blood was collected in winter.

![Figure 2](image1.png)  
**Figure 2.** Influence of years of exposure to benzene-related compounds on biomarkers in the study population. *Significance level < 0.05. **Significance level < 0.005.

![Figure 3](image2.png)  
**Figure 3.** Influence of smoking on biomarkers in smokers and nonsmokers in the study population. PRI, proliferative rate index. *Significance level < 0.05. **Significance level < 0.005.

| Table 4. The effect of confounding factors on various biomarkers in the study population. |
|---|---|---|---|---|---|---|---|---|
| Factor | Number in group | Age | TabF ± SE | AbF | AbC | SCE | PRI | HFC | RAS |
| All | 49 | 41 | 0.044 ± 0.014 | 0.030 | 4.1 | 7.0 | 2.3 | 6.3 | 0.84 |
| Exposure | Unexposed | 25 | 40 | 0.032 ± 0.009** | 0.017** | 3.1** | 6.9 | 2.34 | 6.7 | 0.92 |
| Exposed | 24 | 41 | 0.058 ± 0.018 | 0.045 | 5.3 | 7.2 | 2.28 | 7.0 | 0.74 |
| Smoking | Nonsmokers | 11 | 39 | 0.032 ± 0.010** | 0.019** | 2.9* | 6.6* | 2.31 | 4.3* | 0.53* |
| Smokers | 38 | 41 | 0.047 ± 0.015 | 0.033 | 4.5 | 7.2 | 2.30 | 7.6 | 0.92 |
| Smoking history | Nonsmokers | 11 | 39 | 0.031 ± 0.010 | 0.019 | 2.9 | 6.6** | 2.32 | 4.3** | 0.53** |
| <15/day and <5 years | 6 | 36 | 0.051 ± 0.014 | 0.031 | 4.8 | 6.1 | 2.36 | 2.5 | 1.26 |
| <15/day and >5 years | 19 | 41 | 0.052 ± 0.015 | 0.034 | 4.9 | 7.6 | 2.30 | 8.9 | 1.01 |
| >15/day and <5 years | 2 | 33 | 0.046 ± 0.014 | 0.034 | 4.6 | 7.8 | 2.12 | 7.0 | 0.34 |
| >15/day and >5 years | 7 | 42 | 0.039 ± 0.013 | 0.033 | 3.6 | 7.1 | 2.30 | 9.3 | 0.38 |
| Significantly >15/day and | 4 | 50 | 0.040 ± 0.014 | 0.029 | 3.8 | 6.8 | 2.38 | 4.6 | 1.18 |
| significantly >5 years | | | | | | | | | |
| Sex | Female | 16 | 40 | 0.045 ± 0.013 | 0.025 | 4.3 | 7.5* | 2.32 | 8.5* | 0.77 |
| Male | 33 | 41 | 0.043 ± 0.014 | 0.032 | 4.1 | 6.8 | 2.31 | 6.1 | 0.87 |
| Cancer in immediate family | No | 43 | 40 | 0.042 ± 0.013 | 0.029 | 4.0 | 7.0 | 2.31 | 6.6 | 0.78 |
| Yes | 6 | 40 | 0.054 ± 0.017 | 0.038 | 5.2 | 7.2 | 2.28 | 8.8 | 1.01 |
| Sampling season | Summer | 24 | 40 | 0.033 ± 0.011** | 0.023** | 3.2** | 6.3** | 2.36** | 3.0** | 1.04** |
| Winter | 25 | 41 | 0.059 ± 0.018 | 0.040 | 5.6 | 8.0 | 2.24 | 11.1 | 0.47 |

Abbreviations: TabF ± SE, total aberration frequency (including gaps) ± SE; AbF, aberration frequency (including gaps); AbC, percent of aberrant cells; SCE, sister chromatid exchanges; HFC, percent of cells containing high frequency SCE, i.e., containing number of exchanges above 95% of total in control distribution; PRI, proliferative rate index; RAS, p21 protein levels. *Significance level < 0.05. **Significance level < 0.005.
Variability among the biomarkers in the unexposed subgroup caused by confounding factors is shown in Table 5. Again females showed an increase in levels of SCE and HFC and a decrease for PRI. There was also an influence of season; higher values of SCE and HFC were seen in winter. The various biomarkers for the non-smoking population in relation to exposure are shown in Table 6. There was a statistically significant effect on TAbF, AbF, and HFC due to exposure.

**Discussion**

There are other reports of increases in CA frequencies in lymphocytes of workers exposed to high levels of benzene (2). Our studies have examined the influence of occupational exposure on the various parameters measured in workers from petroleum plants from the central part of Poland. Our results have revealed a significant increase in cytogenetic aberrations in the work population under study and in nonsmoking individuals, but the increase was not correlated with the duration of exposure using recommended statistical procedures (16). Other studies performed in Hungary and Poland also showed significantly higher frequencies of chromosomal aberrations for exposed workers. Again,

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**Table 5.** The effect of various confounding factors on biomarkers in the unexposed subgroup.

| Factor                        | Number in group | Age | TAbF | SE | AbF | AbC | SCE | PRI | HFC | RAS |
|-------------------------------|-----------------|-----|------|----|-----|-----|-----|-----|-----|-----|
| All unexposed                 | 25              | 40  | 0.032| 0.009| 0.017| 3.1 | 6.9 | 2.36| 6.7 | 0.9 |
| Age                           |                 |     |      |    |     |     |     |     |     |     |
| >30                           | 12              | 35  | 0.034| 0.008| 0.016| 3.3 | 6.7 | 2.37| 4.7 | 0.16**|
| >40                           | 13              | 44  | 0.031| 0.010| 0.018| 2.9 | 7.0 | 2.35| 8.3 | 1.3 |
| Sex                           |                 |     |      |    |     |     |     |     |     |     |
| Female                        | 11              | 39  | 0.040| 0.011| 0.019| 3.8 | 7.5**| 2.27**| 8.7*| 0.7 |
| Male                          | 14              | 40  | 0.026| 0.008| 0.016| 2.5 | 6.4 | 2.40| 4.9 | 1.2 |
| Smoking                       |                 |     |      |    |     |     |     |     |     |     |
| Nonsmokers                    | 9               | 37  | 0.025| 0.009| 0.014| 2.3 | 6.5* | 2.32| 3.6**| 0.6*|
| Smokers                       | 16              | 41  | 0.036| 0.010| 0.019| 3.5 | 7.1 | 2.36| 8.5 | 1.1 |
| Smoking history               |                 |     |      |    |     |     |     |     |     |     |
| Nonsmokers                    | 9               | 37  | 0.025| 0.009| 0.014| 2.3 | 6.5**| 2.32| 3.6**| 0.6**|
| <15/day and <5 years          | 4               | 38  | 0.050| 0.012| 0.025| 4.8 | 6.6 | 2.34| 3.8 | 1.1 |
| <15/day and >5 years          | 8               | 42  | 0.039| 0.011| 0.020| 3.8 | 7.7 | 2.30| 9.9 | 1.0 |
| >15/day and <5 years          | 2               | 42  | 0.026| 0.012| 0.015| 2.5 | 7.9 | 2.26| 12.0| 1.5 |
| >15/day and >5 years          | 2               | 44  | 0.007| 0.005| 0.007| 0.7 | 6.6 | 2.57| 10.8| 0.3 |
| Cancer in immediate family    |                 |     |      |    |     |     |     |     |     |     |
| No                            | 21              | 40  | 0.031| 0.009| 0.015| 2.9 | 6.9 | 2.35| 6.6 | 0.9 |
| Yes                           | 4               | 40  | 0.042| 0.014| 0.027| 4.1 | 6.8 | 2.31| 7.1 | 1.2 |
| Sampling season               |                 |     |      |    |     |     |     |     |     |     |
| Summer                        | 15              | 39  | 0.025| 0.007| 0.014| 2.4 | 6.4* | 2.43**| 4.9*| 1.1**|
| Winter                        | 10              | 41  | 0.043| 0.014| 0.023| 4.1 | 7.6 | 2.21| 9.2 | 0.4 |

*Significance level <0.05. **Significance level <0.005.
there was no correlation between aberration frequencies and the duration of exposure to petroleum emissions and benzene (17,18). Results of our studies also revealed an increase in other biological end points investigated in the petroleum-exposed groups. Smoking was also found to affect various biomarkers both in the whole population under study and in the unexposed group, as has previously been shown (19).

A seasonal influence on genotoxic biomarkers in a Polish population has been already observed by Perera et al. (20) and by Anderson et al. (15,21) in a United Kingdom control population. Our data also confirm that there is some seasonal effect on cytogenetic damage, both in the whole population and in the unexposed subgroup where responses are higher in winter. There are various possible reasons for such effects. Environmental pollution might be higher in the winter season due to the intensive combustion of coal for residential heating during the winter months (20), and there are less flora to help remove toxic environmental contaminants. Another reason could be a possible inadequacy in the diet of ordinary Polish people who, in the winter season may be unable to afford sufficient fruit and vegetables containing antioxidant vitamins, which might help protect them from environmental contaminants.

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