Humoral Immunosuppression in Men Exposed to Polycyclic Aromatic Hydrocarbons and Related Carcinogens in Polluted Environments

Andrzej Szczeklik, Jerzy Szczeklik, Zdzislaw Galusza, Jack Musial, Emilia Kolarzyk and Dorota Targosz

1 Departments of Medicine, 2 Occupational Diseases, Jagiellonian University, Cracow, Poland; 3 Social Foundation Solidarnosc, Unit for Immunological and Environmental Diseases, Cracow, Poland

We evaluated humoral immunity by measuring IgG, IgA, IgM, and IgE concentrations in 274 male workers in an iron foundry in Cracow, Poland. There were two groups: 199 coke oven workers and 76 cold-rolling mill workers. The groups were similar with respect to age, length of work (average 15 years), and smoking habits. Exposure to polycyclic aromatic hydrocarbons (PAHs), assessed by personal and area monitoring, ranged from 0.2 to 50 pg/m³ benzo[a]pyrene in coke plant workers and was of 3–5 magnitudes higher than in the cold-rolling mill employees. Comparison of the two groups revealed a marked depression of mean serum IgG and IgA in coke oven workers (p<0.001, Student’s unpaired t-test). In the same subjects, serum IgM had a tendency to decrease, whereas serum IgE showed a trend toward higher values. Thus, workers exposed chronically to complex mixtures of air pollutants, composed primarily of PAHs, develop immunosuppression. It remains to be established whether the immunosuppression described here is related to the frequent development of lung cancer reported in coke plant employees. Workers exposed chronically to PAHs should have serum immunoglobulins monitored regularly.

Key words: benzo[a]pyrene, coke oven plant, immunosuppression, iron foundry, polycyclic aromatic hydrocarbons, serum immunoglobulins. Environ Health Perspect 102:302–304 (1994)

Workers in coke oven plants have a higher incidence of lung cancer than the general population (1–5). They are exposed to a variety of chemicals, in particular polycyclic aromatic hydrocarbons (PAHs), including benzo[a]pyrene (BaP). PAHs are annulated benzene ring compounds formed from the incomplete combustion of organic matter. Coke oven workers are considered a model population for validating PAH–DNA adducts as a marker of biologically effective dose (6,7).

The pathogenesis of cancer development from PAH exposure may be a multifactorial process. In humans, chromosomal aberrations (sister chromatid exchanges) have been observed in peripheral blood lymphocytes of psoriasis patients undergoing treatment with coal tar applications to their skin (8). These patients also excrete PAHs in urine, and urinary PAH levels and chromosomal aberrations can be correlated with the dose of coal tar.

PAHs, known to have carcinogenic activity, also exert immunosuppressive action in experimental animals (9). The immunotoxicity and carcinogenic properties of major PAHs, 7,12-dimethylbenzanthracene, BaP, and 3-methylcholanthrene, have been well documented (5). In mice, dimethylbenzanthracene, BaP and methylcholanthrene suppress antibody production to both T-dependent and T-independent antigens (10). These agents appear to exert their immunosuppressive activity by altering B-cell maturation or function, but defects in T-cell regulation cannot be completely excluded as contributors to the suppression of humoral immunity. Both methylcholanthrene and BaP suppress cytotoxic T-cell activity in mice. Knowledge about the basic mechanisms by which these compounds cause immunosuppression remains incomplete, but the induction of cell transformation by reactive diol epoxides has been postulated as one possible mechanism (11). Another mechanism for the immunosuppressive effects of PAHs might be the induction of aryl hydrocarbon hydroxylase (12), which by inducing cytochrome P450 isoenzymes (13) would lead to generation of the reactive diol epoxides.

The risk of cancer is greater in humans who are immunocompromised. For example, patients who have undergone renal transplantation and post-transplantation immunosuppression to avoid organ rejection have an increased frequency of neoplastic disorders. Patients receiving immunosuppressive treatment for inflammatory diseases such as rheumatoid arthritis show a similar increase in the incidence of lymphoreticular malignancy. Further, children with inborn deficiencies of the immune system have a high incidence of malignant tumors (5). A recent survey reported a striking increase in the malignancies in adult patients with common variable immunodeficiency (14). We are, however, unaware of studies in individuals exposed to PAHs that describe immunosuppression or attempts to link damage to the immune system with carcinogenesis.

We studied 274 male workers employed at the iron foundry of Nowa Huta in Cracow, Poland. The study population consisted of two groups: 199 coke oven workers and 75 cold-rolling mill workers. Subjects were interviewed at enrollment using a standardized questionnaire to elicit occupational, diet, smoking, health and environmental histories. The two groups were similar with respect to age (average, 40 and 48 years, range 19–64 and 32–59 years), percentage of active smokers (71 and 79%), and time of employment (average, 14 and 19 years, range 1.5–35 and 2–39 years); values represent coke oven and cold-rolling mill workers, respectively. Fasting blood specimens were obtained at rest and IgG, IgA, IgM, and IgE were determined by nephelometry (Behring Co., Marburg, Germany).

In 54 workers, personal exposure monitoring was carried out 1 month before the study on 2 consecutive working days (8 hr). Air had been pumped through glass-fiber filters, which were then weighed for total dust content; PAHs after extraction into organic solvents were analyzed by HPLC. We collected stationary samples from each of the major work areas on 2 separate days, and carried out dust and PAH analysis as above. There was good agreement between personal and area monitoring data. The results showed that coke oven workers were exposed to high concentrations of atmospheric PAHs, including fluoranthene, pyrene, chrysene, benzo[a]anthracene, dibenz[a,h]anthracene, and benzo[g,h,i]pyrrole. The workers most exposed to PAHs worked at topside area of coke ovens; the concentrations of BaP varied between 15.0 and 49.0 µg/m³. At the benchside and in the vicinity of coke oven, the values did not exceed 10.0 µg/m³, and were in the range of 0.2–8.0 µg/m³ of BaP. In contrast, in cold-rolling mill workers, BaP concentrations were of 3–5 orders of magnitude lower and remained within the range of 0.001–0.02 µg/m³. Coke oven workers were also exposed to higher concentrations of airborne sulfur dioxide and carbon monoxide than cold-rolling mill workers (3.5–7.9 versus 0.8–2.0 mg/m³ and 3.0–19.5 versus 0.1–0.5 mg/m³, respectively).

Depression of IgG was the most striking finding in coke oven workers. Of coke oven workers, 21.5% had serum IgG ≤1.000 mg/dl as compared to only 9% of cold-rolling mill workers (Fig. 1). The distinctly diminished serum IgG levels, below 700 mg/dl, were present in 5% of the workers.
oven workers versus 1.5% of the cold-rolling mill workers. A similar difference in serum IgA, but not in IgM or IgE, was also evident between the two study groups (Table 1). We analyzed goodness-of-fit of observed frequencies of all four serum immunoglobulin distributions using a chi-square test; despite some skewness, all four immunoglobulins fitted better with log-normal than normal distribution. The subsequent analyses were therefore performed on a log-transformed scale. Mean serum IgG and IgA concentrations were significantly lower in coke oven as compared to cold-rolling mill workers [ln(IgG) = 7.14 ± 0.35 versus 7.34 ± 0.28, p<0.001; ln(IgA) = 5.42 ± 0.40 versus 5.62 ± 0.39, p<0.001; unpaired Student’s t-test]. Mean IgM levels showed a tendency toward lower values in coke oven workers, which, however, did not reach significance [ln(IgM) = 4.93 ± 0.47 versus 5.02 ± 0.42, p=0.05]. In contrast, mean IgE was moderately higher in coke oven workers, though this could be a chance observation [ln(IgE) = 4.17 ± 0.84 versus 3.96 ± 1.13, p = 0.13]. In either study group, no correlation was found between the length of exposure and serum immunoglobulin levels. There was no relationship between serum IgG and IgA levels in the coke workers.

Our results point to immunosuppression in men exposed chronically to PAHs. The exposure experienced by our subjects was a marked one. Such levels of exposure have been radically decreasing in the last few years (15). Still, values of BaP similar to those recorded in our study were reported in a coke plant by other investigators over the last two decades (16). At pitch batteries and at the roof of ovens, concentrations of BaP between 10 and 60 µg/m³ were described, while at or near the bottom of the ovens levels rarely exceeded 5 µg/m³. Some categories of workers, such as wharfman or jamb cleaners, are more exposed than car operators or door cleaners. The length of exposure is not, therefore, the only risk factor. This might explain why we have not observed relationship between duration of employment at the coke plant and degree of immunosuppression. Another explanation might be difference in genetic susceptibility: accurate methods for assessment of genetic susceptibility are being developed and might soon be used to detect persons susceptible to environmental hazards (15,17).

It might be assumed that the major culprit for immunodeficiency here described was PAHs. Their immunotoxic effects have been well documented in experimental animals, but not yet in humans. The immunotoxic effects of PAHs could have been potentiated by chronic inhalation of SO₂ and CO arising during the process of coal combustion. In experimental animals exposed for several months to SO₂ and coal dust, significant immunosuppression is observed (18). Finally, the majority of the subjects we studied were heavy smokers, and tobacco smoke leads to the formation of aromatic DNA-adducts in heart and lung tissue and also in blood lymphocytes (19).

In our coke plant workers, biosynthesis of IgG and IgA was markedly depressed, whereas IgM showed a tendency to decrease, though this did not reach statistical significance. On the other hand, serum IgE had a trend toward increased values. Such a contrasting response of IgE as compared to other immunoglobulins was observed after ischemic injury in men (20). A positive correlation between the total IgE concentration and both outdoor air pollution and active tobacco smoking have been reported (21).

In summary, our study demonstrates that coke oven workers exposed chronically to complex mixture of air pollutants compose primarily of PAHs develop immunosuppression, which is characterized by depression of serum levels of IgG and IgA. It remains to be established whether the immunosuppression described here is related to the frequent development of lung cancer reported by other authors (1–5) in coke plant employees. Such a relationship might be deduced from Burkitt’s theory of “immune surveillance,” namely, that a defective immune system leads to an increased incidence of cancer. A practical conclusion of the study is that workers exposed chronically to PAHs should have serum immunoglobulins levels monitored regularly.

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**Table 1. Serum immunoglobulins in the two populations studied**

| Immunoglobulin | Coke oven | | | | | Cold rolling mill | | | |
|----------------|-----------|-----------|-----------|-----------|-----------|------------------|-----------|-----------|-----------|
|                | Range     | Median    | Arithmetic| Geometric | SD        | Range            | Median   | Arithmetic| Geometric |
| IgG (mg/dl)    | 427–2915  | 1330      | 1353      | 1289      | 411       | 651–3770         | 1560      | 1613      | 1551      | 468       |
| IgA (mg/dl)    | 27–687    | 216       | 250       | 230       | 115       | 101–588          | 275       | 295       | 276       | 109       |
| IgM (mg/dl)    | 26–710    | 138       | 157       | 140       | 88        | 65–414           | 152       | 164       | 151       | 67        |
| IgE (IU/ml)    | 32–1032   | 44        | 113       | 91        | 167       | 1–400            | 39        | 93        | 80        | 108       |

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**Figure 1. Results of individual IgG determinations.** Horizontal bars represent geometric means.
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