

Occupational Health / Safety in the World

Story of Benzene and Leukemia: Epidemiologic Approach of Muzaffer Aksoy

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Abstract: Story of Benzene and Leukemia: Epidemiologic Approach of Muzaffer Aksoy: Fusun YARIS, et al. Karadeniz Technical University, School of Medicine, Department of Family Medicine, Turkey—In 1974, Professor Muzaffer Aksoy established a link to leukemia in humans as a result of occupational exposure to benzene. The aim of this study is to evaluate his epidemiological approach for his investigation on the effects of benzene and to bring attention to the benzene problem in Turkey. Dr. Aksoy observed that a large group of leukemic patients were shoemakers, or they worked in leather manufacturing. In the 1960s, benzene was a popular solvent in the leather industry. Dr. Aksoy conducted a field investigation in Gedikpasa- Istanbul, where the shoemakers worked so that he could draw his key observations from actual environmental conditions. With a gas detector, he found the concentration of benzene in these work places to be 150–210 ppm and up to 650 ppm on rare occasions. He performed an epidemiological study and health education among 28,500 shoe, slipper and handbag workers during the period from 1967 to 1974. He published these data, establishing an association between benzene and leukemia. The incidence of leukemia among the shoe workers was decreased by screening, health education, and legislative actions in Turkey, but it began to increase again because of lack of an occupational health policy and underestimation of the problem. These results suggest the importance of primary prevention of occupational cancers. Dr. Aksoy's epidemiologic approach may highlight the necessity for detailed investigations of the occupational status of patients who need medical aid in order to diagnose

the real underlying factor.
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Chemical exposures that occur in the workplace may cause cancer. This has been known since Percival Pott, 1775. The role of the occupational epidemiologist is to collect data that will permit judgments to be made about whether a substance at some defined level of exposure does or does not present a risk for cancer and/or other diseases¹. Measurement of exposure depends on the nature, dose, and period of the exposure². Very few studies have been conducted of exposure to occupational carcinogens in developing countries, and even fewer studies have examined the health consequences of such exposures. There is, however, growing concern that the health impact of many chemicals used in the developing world has been underestimated³.

According to the evidence of carcinogenicity in humans, the occupational agents are categorized into four groups: i) sufficient evidence, ii) limited evidence, iii) insufficient evidence and iv) lack of evidence of carcinogenicity in humans. Occupational exposure to benzene and its carcinogenicity in humans is well-established^{1–4, 5}.

In 1825, Michael Faraday isolated a new substance from a gas used at that time for illumination. This compound, now called benzene (C₆H₆), was an example of a new class of organic substances called aromatic compounds. According to Mansfield and Hofmann⁶, benzene was originally produced in 1848 from coal tar. In 1987, Santesson reported a case of aplastic anemia and Le Noire and Claude reported a case of acute leukemia due to chronic exposure to this chemical⁷. The

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stories of these case reports were summarized by Dr. Aksoy and he mentioned that “benzene has been a suspected leukomogenic and carcinogenic agent”⁷⁾. Up to 1974, some case reports or patient series were published in the medical literature, but these reports depended only on clinical findings and not on an epidemiological method. A Turkish haematologist, Professor Muzaffer Aksoy conducted an epidemiologic study and reported his findings clearly showing a relationship between benzene and leukemia, in 1974⁵⁾.

The aim of the present study is to evaluate the bibliographic professional life and epidemiologic approach of Dr. Aksoy, who conducted epidemiological and clinical investigations on the effects of benzene in shoe and leather workers.

History

Alert clinicians have historically been the first to identify occupational cancers¹⁾. Professor Aksoy was an expert, open-minded clinician⁸⁾. He was born in 1915 and graduated with honors from the Istanbul University, School of Medicine in 1940 during the “Second World War.” During his graduation speech that he gave on behalf of all graduates, he said, “My actual life is beginning under the voices of the guns all over the world”⁹⁾. In 1946, he completed his residency in internal medicine at Istanbul University’s Capa Medical School. In his first position with the Mersin State Hospital, he focused his research on beta-thalassemia and discovered Eti-Turk Hemoglobin that is frequent in the Mediterranean Region of Turkey. In other words, his first study was an ethnopediologic work.

In 1952, Dr. Aksoy traveled to the USA to work in the Department of Haematology at the New England Hospital Center with Professor William Damashek, the founder of that department. While in the USA, he was involved in a project on fetal hemoglobin; the results of this project were published in *Acta Haematologica* in 1955. Dr. Aksoy returned to Turkey in 1953¹⁰⁾.

In 1959, Dr. Aksoy accepted an Associate Professor position with Istanbul University in the Department of Haematology at the Capa School of Medicine. In his clinic, he frequently observed leukemia cases at a higher than expected rate; at that time, the prevalence of leukemia in the population was 4/100,000⁹⁾. He decided to investigate the common subject of these cases and remembered Bernardo Ramazzini’s advice: “Ask the occupation.”¹¹⁾ He observed that a large group of leukemic patients were shoemakers, or they worked in leather manufacturing¹¹⁾. He hung up his white laboratory coat, left his office, and went to the field in Gedikpasa, where shoemakers worked in unhygienic conditions¹¹⁾. He began to draw key observations from the environmental conditions of the workers. Since 1955 in Istanbul, benzene had been used as a solvent in the

manufacturing process¹²⁾, and throughout the 1960s, benzene remained a popular solvent in the leather industry. One reason for its popularity is the fact that it had a nice smell, which the workers enjoyed¹³⁾. In addition, benzene was a major component of the glue commonly used in the shoe making process¹¹⁾. With a gas detector, Dr. Aksoy found the concentration of benzene in these work places to be 150–210 ppm, and up to 650 ppm on rare occasions¹⁴⁾.

Dr. Aksoy and his associates performed an epidemiological study and health education among 28,500 shoe, slipper, and handbag workers in Istanbul from 1967 to 1974^{14,15)}. During this period, 31 leukemic individuals were detected among this group of workers¹⁵⁾. In 1971, he reported blood dyscrasias due to chronic benzene toxicity such as leucopenia, thrombocytopenia, pancytopenia and aplastic anemia in workers, particularly shoe workers in Istanbul¹⁶⁾. The crude incidence of leukemia in these shoe workers was 13.59/100,000, which is significantly higher than the leukemia incidence of 4/100,000 in the general population in Istanbul. The incidence of leukemia among the population of Turkey was between 2.25 and 2.80/100,000¹⁷⁾. The annual number of leukemic shoe workers in Istanbul was 1, 1, 3, 4, 6, and 5, respectively between 1967 and 1972. The peak incidence of leukemia among the shoe workers in Istanbul was recorded in 1973 with 7 new cases¹⁸⁾.

After the prohibition and discontinuation of the use of benzene in Turkey, a striking decrease was observed in the number of leukemic shoe workers. The number of new leukemic shoe workers decreased between 1974 and 1975 to the level noted between 1969 and 1970 (i.e., 4 and 3 cases, respectively), and none were reported in the subsequent three years¹⁹⁾. In 1974, he was appointed full professor. In 1975, Dr. Aksoy was invited to the U.S. Supreme Court of Industry as a scientific expert to provide his scientific findings regarding the health effects of benzene exposure in the workplace. These hearings lasted almost one year and resulted in the legal maximum permissible concentration of benzene being decreased to 1 ppm in the USA^{11, 12)}. The Japan Society for Occupational Health recommends a reference value for benzene of 1 ppm²⁰⁾.

Ten years later, Dr. Aksoy performed another study with one of the present authors²⁰⁾. Unfortunately, this study showed that despite the considerable decrease in the content of benzene in solvents and thinners available in Istanbul and Izmit, the percentages of benzene in most industrial materials was still above permissible limits²¹⁾. In this study, Dr. Aksoy noted that leukemia began to increase among the shoe workers in Turkey in 1979. He thought that the reappearance of leukemia after 1979 in Istanbul and other cities of Turkey may be attributed either to the individual variation of the interval between the occurrence of leukemia and exposure to the chemical, or

to the continuing use of solutions containing benzene²¹). He continued to report new cases²²) and reported that in 23.7% of his series, consisting of 59 leukemic patients with benzene exposure, there was a preceding pancytopenic period. Furthermore, he found a familial connection in 10.2% of them, and that 89.8% of the cases showed findings of acute leukemia. He discussed the possible factors that might determine the types of leukemia attributable to benzene toxicity¹⁹). He discussed other malignancies attributable to chronic exposure to benzene²³). In 1990, he continued to report that the benzene problem was not completely solved in Turkey because of the lack of an occupational health policy and because the problem had been underestimated²⁴). For almost 40 yr until his death in 2001, he worked on determining the effects of benzene.

Discussion

The general design of epidemiological studies contains descriptive and analytical stages^{25–27}). Components of the descriptive stage are: i) deciding on the research question, ii) identifying the homogenous and similar cases, iii) collecting all data on all cases, and iv) investigating the existential patterns and trends of the diseases. Components of the analytic stage are: i) making an hypothesis (etiology) and planning the study; ii) performing the study, obtaining data, and analyzing the data; iii) generating the results; and iv) developing comments and reports^{25–27}).

When we evaluate Dr. Aksoy's approach based on the general design of an epidemiological study, we determined that Professor Aksoy had documented an unexpected high frequency of leukemia in patients exposed to benzene. He identified the common occupational status of these cases and also found homogenous and similar cases. He described the existing patterns and developing trends of the disease. He visited the work places of the patients, collected data, and analyzed these data. He reported his results and made comments and suggestions on the causal relationship between benzene and leukemia. Interest in his work was generated all over the world. He received about 1,000 national and international citations for his studies on benzene.

Because of his work, legislative actions were taken all over the world, which resulted in a decrease in the incidence of leukemia due to benzene exposure.

Quantitative risk evaluation of environmental carcinogens is required not only for their regulation but also for primary cancer prevention²⁸). Professor Aksoy's efforts to provide health education to the workers resulted in successful primary prevention of leukemia, but unfortunately, benzene is still an emerging problem in Turkey as he reported²⁴).

In a conversation in 1987, a scientific journalist asked

Dr. Aksoy about the importance of money in research. He answered: "Anyone can do research under austere conditions with only minimal funding if the researcher really wants to do the work. The research can be conducted on a small scale, but even that can contribute to science. The key is the researcher's enthusiasm."²⁹). One of his friends wrote that Dr. Aksoy had received only 100 USD for his work on Hemoglobin-Istanbul³⁰), but as a result of his research, he received many national and international scientific awards, including the "Ramazzini Award"³¹). Dr. Aksoy's wife of sixty years provided a better understanding of the problems he faced in conducting his research when she reminded us of the difficult times in Turkey during the first decades of the new Turkish Republic in addition to the ramifications of World War II. However, because of his dedication and enthusiasm, Dr. Aksoy worked very hard for his patients and country"³²).

Conclusions

Professor Aksoy, as an astute clinician hematologist, identified the association between benzene and leukemia more than thirty years ago. The increasing incidence of leukemia among shoe workers suggested the need for legislation. The incidence was decreased by his primary prevention and screening efforts, health education and legislative actions.

His epidemiologic approach may highlight the necessity for skeptical and scientific thinking regarding the occupational situations of patients who are seen in clinical practice.

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