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Benzene and leukemia: from scientific evidence to regulations. A historical example

Michael Belingheri[1], Silvia Fustinoni[2,3], Giovanni De Vito[1], Alessandro Porro[2], Michele Augusto Riva[1]

[1] School of Medicine and Surgery, University of Milano-Bicocca, Monza, Italy
[2] Department of Clinical Sciences and Community Health, University of Milan, Milan, Italy
[3] Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico, Milan, Italy

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Parole chiave: Benzene; leucemia; Vigliani; Forni; Clinica del Lavoro; Milano; esposizione occupazionale; tossicologia industriale; storia

Summary

Background: *Benzene is a highly flammable, highly volatile liquid aromatic hydrocarbon. It has been used in many industrial processes as a solvent or a starting material. At the beginning of the twentieth century, it was very widely used in the workplace, especially in printing and in the shoe manufacturing and rubber industries. Although benzene was first recognized to cause aplastic anemia, its association with leukemia has been investigated only since the 1930s. In 1963, Italy was one of the first countries in the world to adopt a law to ban benzene as a solvent in work activities.* **Objectives:** *This study analyzed the contribution of the Clinica del Lavoro in Milan, Italy, to studies of the relationship between exposure to benzene and leukemia.* **Methods:** *Scientific literature and historical sources on benzene and leukemia in the twentieth century were reviewed, and interviews with a first-hand witness of that period were conducted.* **Results:** *By 1928, several scholars had reported anecdotal cases of leukemia among workers exposed to benzene. Enrico Vigliani was the first to collect all of these cases and to try to conduct statistical analysis on these data, in order to support the association between benzene and leukemia. In the 1960s, Vigliani and Alessandra Forni showed that benzene could cause chromosome aberrations in the bone marrow that could produce leukemic clones.* **Conclusions:** *As a result of these studies and the subsequent regulations which banned benzene, exposure conditions changed in the workplace in the last few decades. The resulting low concentrations have prompted researchers to investigate new exposure biomarkers and to study any related health problems.*

Riassunto

***«Benzene e leucemia: dall'evidenza scientifica alla normativa. Un esempio storico»*. Introduzione:** *Il benzene è un idrocarburo aromatico, liquido, altamente infiammabile e volatile. È stato utilizzato in molti processi industriali come solvente o materia prima. All'inizio del ventesimo secolo, era largamente in uso nei luoghi di lavoro, specialmente nella stampa, nella produzione di scarpe e nell'industria della gomma. Sebbene il benzene sia stato riconosciuto precocemente come causa di anemia aplastica, la sua associazione con la leucemia è stata studiata solo a partire dagli*

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Corrispondenza: Michael Belingheri, MD, School of Medicine and Surgery, University of Milano-Bicocca, Building U38 (Villa Serena), Via Cadore 48, Monza, Italy - Tel. +39 0264488191 - E-mail: michael.belingheri@unimib.it

anni '30. Nel 1963, l'Italia è stato uno dei primi paesi al mondo ad adottare una legge per vietare l'uso del benzene come solvente nelle attività lavorative. **Obiettivi:** *Questo studio ha analizzato il contributo della Clinica del Lavoro di Milano agli studi sulla relazione tra esposizione a benzene e leucemia.* **Metodi:** *Sono state revisionate la letteratura scientifica e le fonti storiche su benzene e leucemia nel ventesimo secolo e sono state condotte interviste a un testimone di quel periodo.* **Risultati:** *Fino al 1928, diversi studiosi avevano riportato casi aneddotici di leucemia tra lavoratori esposti al benzene. Enrico Vigliani è stato il primo a raccogliere tutti questi casi e cercare di condurre delle analisi statistiche su questi dati, al fine di provare l'associazione tra benzene e leucemia. Negli anni '60, Vigliani e Alessandra Forni dimostrarono che il benzene poteva causare aberrazioni cromosomiche nel midollo osseo che potevano produrre cloni leucemici.* **Conclusioni:** *Come risultato di questi studi e della successiva normativa che ha vietato il benzene, le condizioni di esposizione negli ambienti di lavoro sono cambiate negli ultimi decenni. Le conseguenti basse concentrazioni hanno spinto i ricercatori a studiare nuovi biomarcatori di esposizione e a considerare eventuali problemi di salute ad esse correlati.*

Background

Benzene (C_6H_6, CAS 71-43-2) is the simplest aromatic hydrocarbon. It is a clear, colorless, highly flammable and highly volatile liquid chemical with a gasoline-like odor (32). It was first isolated by the British scientist Michael Faraday (1791-1867) in 1825, who separated it from a complex mixture obtained as a by-product of illuminating gas production (33).

Today benzene is one of the major products of the petrochemical industry worldwide. In the past, benzene was used as a component of inks in the printing industry, as a solvent for organic materials, and as starting and intermediate material in the chemical and drug industries (the manufacture of rubbers, lubricants, dyes, detergents and pesticides). Today, the primary use of benzene is in the manufacture of organic chemicals such as styrene, ethylbenzene, cumene, cyclohexane, and phenol which are further used to produce polymers (26).

Workers can be exposed to benzene in workplaces where it is produced or used. Additionally, workers and the general population can be exposed to benzene in gasoline vapors and in vehicular exhaust fumes, as benzene is an impurity in the aromatic mixture added to improve the anti-knocking power of unleaded gasoline. Finally, exposure to benzene is associated with both active and environmental tobacco smoking (4, 19).

It is universally acknowledged that human exposure to benzene is associated with a range of acute and long-term adverse health effects and diseases, including cancer and aplastic anemia (51). Several studies conducted in the mid-twentieth century identified and confirmed the association between benzene and leukemia.

At the beginning of the twentieth century, workers were exposed to high concentrations of benzene during their activities in the workplace and at home, where many people used to work. In those years, the pathogenic relationship between benzene exposure and leukemia was not known. However, studies had already shown that chronic benzene poisoning could affect the bone marrow, resulting in marked hypoplasia (2). In fact, several cases of aplastic anemia and aplastic bone marrow were described in workers exposed to benzene. Some studies even reported the use of benzene in the treatment of leukemia for its ability to reduce bone marrow activity. Benzene appeared to be effective especially if used after x-ray therapy (1). Benzene was mainly administered in gelatin capsules with an equal quantity of olive oil during or immediately after a meal to reduce side effects, especially gastric disorders (2). Like other methods used at that time, benzene provided only temporary benefits in the treatment of leukemia (2).

In addition to aplastic anemia, other hematologic disorders in people exposed to benzene started to be described in the 1920s, leading to the suspicion that this substance could also cause leukemia. In 1928, Delore and Borgomano reported the first case of benzene-related leukemia in a man who had worked at a pharmaceutical manufacturing plant for fifteen

years, the last five of which were in a job where he experienced excessive benzene exposure (9). Three years later, Martland described in a letter an unusual case of leukemia related to occupational exposure to benzene (23). In 1932, Emile-Weil reported the case of a woman who died from leukemia and who was exposed to benzene in a rubber factory (50). In 1934, Thompson, Richter and Esdall described a new case of leukemia in a man exposed to a large quantity of benzene (43).

Until the first half of the 1930s, benzene-related leukemia was only anecdotally described in the international scientific literature. As Alice Hamilton (1869-1970) stated: "The victims of industrial [benzene] poisoning whose bodies have come to autopsy are few in number, and their cases have not received a careful study, except in rare instances" (23).

In a renowned paper from 1938, the Italian physician Enrico Vigliani was the first to systematically review all the anecdotal case reports and postulate the relationship between benzene exposure and leukemia (35).

First studies by Enrico Vigliani in Turin and Milan

Enrico Carlo Vigliani (1907-1992), director of the Clinica del Lavoro in Milan from 1942 to 1977, was a well-known personality in the field of occupational health in the twentieth century (36, 45). In 1938, Vigliani, together with Fausto Penati (1904-1984), conducted a critical review on the hematologic effects of benzene, analyzing all the cases described at the time in the scientific literature. They summarized all the descriptions of blood disorders in workers exposed to benzene, thus providing evidence that aplastic anemia was not the only hematologic condition related to the solvent. They also described experimental studies conducted on animals that confirmed these observations. Vigliani and Penati concluded that chronic exposure to benzene could affect the bone marrow in different ways, and therefore could cause different hematologic disorders including leukemia (35). It should be noted that the importance of this paper – written in Italian and hence not well-known internationally – was confirmed by the words of Alice Hamilton who cited its results when she stated that evidence seemed to be accumulating, and "that leukemia may be one of the forms benzene poisoning may take" (21, 22).

In 1945, Giulio Saita, who worked with Vigliani in Milan, reported the first case of leukemia where benzene concentrations could be dosed in indoor air, in the workplace of a rotogravure worker who used a 40% benzene solution to clean cylinders (40).

Vigliani and his team sought to understand whether benzene-related aplasia and leukemia could be connected, supporting two alternative hypotheses to explain this ambivalence. First, hyperplasia and subsequent leukemia could be secondary to aplasia, as a compensatory mechanism. Second, aplasia could instead be secondary to leukemia, due to mechanical compression or to replacement by leukemic tissue. They concluded that benzene could induce primary hyperplasia and leukemia, although in some cases aplasia appeared to be the first step in the process (39, 40, 41). The reason for some people being affected by aplasia or leukemia with the same benzene exposure was unknown; it could depend on dose, route of intake or the characteristics of individuals and tissues.

This aspect appeared very important for the recognition of leukemia as an occupational disease. In Italy since the 1930s compensation existed for only six occupational diseases, including those caused by benzene exposure, but with specific reference to only anemia, hemorrhage, and neuritis (27). In reality, some cases of leukemia were compensated due to the simultaneous presence of aplastic disorders in the bone marrow. In 1945, Saita proposed a modification to insurance legislation to include leukemia as an occupational disease in workers exposed to benzene (40). In light of scientific results, the 1952 reform of the Italian compensation system for injuries and occupational diseases recognized all diseases caused by benzene, including leukemia, as occupational (28).

In subsequent years, Vigliani and his colleagues studied the histotype composition of leukemia caused by benzene. They noticed that no cases of chronic myeloid or lymphocytic leukemia were included; in the international literature, the incidence of chronic leukemia was lower than acute leukemia

(44). Moreover, in cases of chronic leukemia, benzene exposure was not clearly documented (47). They therefore concluded that benzene caused mainly acute or subacute leukemia, and particularly acute myeloid leukemia (41). In 1964, Vigliani and Saita tried to estimate the role of benzene exposure, providing evidence that the number of cases of leukemia among exposed workers was about twenty times higher than in the general population (46). They concluded that benzene could induce both aplastic anemia and leukemia, even given a long latency period from the time of exposure (46).

The ban of benzene as a solvent in work activities

These studies provided evidence that chronic exposure to benzene could be related to not only acute occupational poisoning but also leukemia, even fatal in some cases. Nevertheless, the use of benzene as a solvent in work activities was still allowed in Italy.

The main work activities affected by benzene exposure were shoe manufacturing and rotogravure. In Vigevano in the province of Pavia in particular, there were shoe manufacturers that used glues containing benzene in their process. Some phases in shoe manufacturing were performed at home, and therefore the entire family – including children – could be similarly exposed to benzene vapor from glues.

During the spring of 1962, there was an outbreak of benzene poisoning, with tens of cases of poisoning in the factory workers of Vigevano. There were several deaths, including one child. This event had an impact on public opinion, as described in the Italian press of the time (6, 7). A large strike involved hundreds of shoe factory workers who requested a ban on benzene (8).

The Italian parliament was forced to take action and few months later, in the proposal of a new law, it expressly considered studies on the effects of benzene by "distinguished doctors and scientists" including Vigliani (34) and the team of Salvatore Maugeri (1905-1985) at the University of Pavia (30, 31). In a paper published in 1964, Vigliani himself acknowledged their contribution in this field, stating "we are indebted to […] to Professor Salvatore Maugeri, director of the Institute of Occupational Health of the University of Pavia, who gave us information about the cases of benzene myelopathy seen at his institute" (46).

In 1963, as a result of the studies conducted by these "distinguished doctors and scientists", Italy was one of the first countries in the world to adopt a law to ban benzene as a solvent in work activities (Law 245/1963).

The study of chromosome disorders and the final acknowledgment of the International Agency for Research of Cancer

In the 1960s, new techniques for studying the chromosomes of human somatic cells allowed the investigation of alterations to the human chromosome complement by exogenous agents (15, 16). The Clinica del Lavoro directed by Vigliani made relevant contributions in this field, mainly due to the work of Alessandra Forni who received her training in molecular biology at Memorial Sloan-Kettering Cancer Center in New York (14, 36, 47). Forni was the first scientist to study chromosome disorders in people exposed to benzene. She provided evidence that the changes caused by benzene to bone marrow were nonspecific and similar to those caused by ionizing radiation, another occupational cause of leukemia (48). These studies also showed that benzene exposure could cause both stable and unstable chromosome aberrations (17, 48). These alterations might give origin to abnormal clones in the bone marrow, one of which might become a leukemic clone (10, 11). Moreover, the rate of chromosomal changes in the peripheral blood lymphocytes of exposed workers was higher than in controls, even in the absence of signs of bone marrow damage. Indeed, there was a high frequency of chromosome aberrations in the bone marrow cells of patients with benzene hematologic disorders (48). For each subject, cells were stimulated to divide using phytohemagglutinin and then one hundred metaphases were directly counted and scored for chromosome aberrations (13), often by Forni herself with no other support.

Chromosome damage could be present for years after cessation of exposure and recovery from benzene poisoning (13). The studies were conducted on

T-lymphocytes because their lifetime is longer than B-lymphocytes. In this way, Forni was able to find out chromosome damages, which were primarily chromosomal breaks (16).

Vigliani and Forni put forward the hypothesis that peripheral blood lymphocyte disorders could be an indicator of past exposure to benzene, after excluding exposure to other possibly confounding agents (48). They also showed that exposing workers to toluene and xylene – which replaced benzene in some industrial activities after the ban – failed to produce a significant increase in chromosomal aberrations (12, 48, 49).

Both these studies on DNA damage and the previous studies by Vigliani and his team were very important in establishing the relationship between benzene exposure and leukemia. The International Agency for Research on Cancer (IARC) working group in charge of preparing the first monograph on benzene reviewed the worldwide literature, including studies by Vigliani and his colleagues, to look into the carcinogenicity of this chemical substance. In 1974, IARC Monograph No. 7 concluded that based on human data, benzene might damage the hematopoietic system (24). In 1982, IARC Monograph No. 29 considered new scientific evidence, including the latest contributions by Vigliani. This monograph stated that there was sufficient evidence of benzene carcinogenicity to man, and included benzene in IARC group 1 as a known carcinogen to humans (25). This conclusion was reiterated in 2018 in Monograph No. 120, in which the carcinogenicity of benzene was confirmed on the basis of sufficient evidence in humans, sufficient evidence in experimental animals, and strong mechanistic evidence (29).

Conclusions

Physicians and researchers at the Clinica del Lavoro, directed by Enrico Vigliani, contributed to clearly defining the relationship between benzene exposure and leukemia and to increasing the awareness of the risks of using benzene. Once the relationship had been defined, Vigliani continued his studies on benzene, focusing on the specific damage to the bone marrow. Pioneering contributions were also made by Alessandra Forni, who was the first in the world to study chromosome aberrations in people exposed to benzene (18). These studies contributed to the decision to ban benzene as a solvent in work activities in Italy, and established the relationship between benzene exposure and leukemia. In fact, in the 1970s and 1980s these works were reported in IARC monographs, supporting the concept of benzene as carcinogenic to humans (group 1) (24, 25). Finally, two studies written by Alessandra Forni and Luciano Moreo in the 1960s (10, 11) were referenced in the latest IARC monograph published in 2018 (26), thus confirming their importance in the history of the study of the relationship between benzene and leukemia.

As a result of the regulations which ban benzene, exposure conditions have changed in the workplace (38) in the last few decades. Today, the main sources of benzene are vehicle exhaust and other combustion processes. Low concentrations have prompted researchers to investigate new exposure biomarkers and to study any health problems, using very specific and sensitive assays based on novel techniques such as mass spectrometry and new approaches such as molecular biology. Again, the Clinica del Lavoro continues to play an important role in the research on benzene, especially in the field of epigenetic studies (3, 5, 20, 38, 42), thus picking up the baton from Enrico Vigliani and Alessandra Forni.

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Necrologio/Obituary

Sven Hernberg, 1934-2019

La Medicina del lavoro italiana ricorda con sincero affetto il Professor Sven Hernberg, deceduto il 10 giugno 2019 all'età di 85 anni.

Hernberg ha lavorato al *Finnish Institute of Occupational Health* (FIOH) per più di 30 anni e per la maggior parte della sua vita professionale ha operato come professore e direttore del Dipartimento di Epidemiologia e Biostatistica. Come direttore scientifico ha contribuito a rendere FIOH uno dei principali istituti di ricerca sulla salute negli ambienti di lavoro.

Il suo contributo alla ricerca e alla formazione epidemiologica, sia a livello nazionale che internazionale, è stato incommensurabilmente importante.

Ha partecipato a numerosi organi scientifici nazionali e internazionali.

È entrato a far parte della *International Commission on Occupational Health* (ICOH) nel 1970, sotto la Presidenza di Enrico C. Vigliani, e ne è stato vice-presidente dal 1981 al 1987, presidente dal 1987 al 1993, e dal 2000 ha ricoperto il ruolo di Past-President e Board Member. In qualità di vice-presidente, ha rinnovato il sistema dei Comitati Scientifici di ICOH e, come Presidente, ha rinnovato la Costituzione ICOH e gli statuti. Durante la sua presidenza, è stato lanciato il primo codice deontologico ICOH per professionisti della salute professionale. Insieme agli organizzatori nazionali e al Segretario generale di ICOH, Luigi Parmeggiani prima e Jerry Jeyaratnam poi, ha guidato l'organizzazione di cinque congressi ICOH e migliorato sostanzialmente il loro peso scientifico. Sven è stato nominato Membro Onorario di ICOH nel 2000 ed è stato premiato con il "Centennial ICOH Award" nel Congresso ICOH nel 2006.

Verso la metà degli anni settanta ha fondato *The Scandinavian Journal of Occupational Health* di cui è stato redattore capo dal 1975 al 2000 e redattore emerito dal 2000 al 2004. Sotto la sua guida, il giornale è diventato una delle principali riviste scientifiche nell'ambito della ricerca in medicina del lavoro. Ha organizzato corsi avanzati di epidemiologia in Finlandia e nei paesi nordici, addestrando un'intera generazione di epidemiologi occupazionali. La sua attività di ricerca ha contribuito alle conoscenze sulla tossicologia dei metalli e ha affrontato le più svariate tematiche della medicina del lavoro quali patologie da solventi, tumori professionali e monitoraggio biologico

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