4. Benzene: an historical perspective on the American and European occupational setting

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4.1. Early warnings

Since the 1897 report of Santessen, who observed aplastic anaemia among young women engaged in the manufacture of bicycle tyres in Sweden, and the report in the same year by LeNoir and Claude, who observed haemorrhaging in a young man engaged in a dry-cleaning operation in France, benzene has been known to be a powerful bone marrow poison. Similar reports of workers developing benzene-related diseases of the bone marrow increased dramatically through the first half of the 20th century.

Between 1910 and 1914, the first major use of benzene as a solvent in the rubber industry took place. Production of benzene was also stimulated greatly by the demand for toluene in the manufacture of explosives during the First World War. Expanded use of benzene in industry after the war led to an increased use of benzene as a solvent in the artificial leather industry, rubber goods, glue manufacturing, hat manufacturing, rotogravure printing, paint, adhesives, coatings, dry cleaning, automobile manufacturing, tin-can assembly, as a starting material in organic synthesis, in petroleum products and in the blending of motor fuels.

This expansion in the industrial uses of benzene was accompanied by a vast increase in the numbers of reported cases of aplastic anaemia, generally referred to as 'benzene poisoning'. Some individuals were diagnosed with benzene poisoning within a few weeks of initial employment and some died within a few months of beginning their jobs (Hogan and Schrader, 1923). These poisonings were associated with benzene levels ranging mostly between 200 ppm (parts per million) and 1 000 ppm. Greenburg and colleagues (1926) made a survey of 12 plants in the United States that used benzene and observed that 32 % of the workers had abnormally low white blood cell counts (below 5 500 per cc), and 12 % had below 4 000 per cc. The benzene exposure levels associated with this extremely high prevalence of abnormal white blood cell counts were 90 ppm and higher. Greenburg (1926) recommended medical removal if an employee developed clinical symptoms of poisoning, or if blood values for individual workers dropped 25 % or more.

Glossary

Leukaemia: a progressive cancer of the blood. It can be classified clinically by duration of the disease (acute or chronic), and by character of the disease, including myelogenous (myeloid cells in excess; lymphatic (lymphoid cells in excess); monocytic (monocytes in excess)

Aplastic anaemia: a condition whereby the bone marrow fails to produce enough red blood cells, white blood cells and platelets. Therefore the individual is usually tired because there are not enough red blood cells available, is susceptible to infection because there are not enough white blood cells present, and bleeds easily because there are not enough blood platelets available

Benzene poisoning: usually refers to aplastic anaemia

Hypersusceptibility: a condition of increased susceptibility to toxic exposures in relation to the average person

Haemopathy: an abnormality of the blood

Multiple myeloma: a cancer of the lymphatic system

4.1.1. First report of benzene-induced leukaemia

In 1928, Dolore and Borgomano published the first case of benzene-induced leukaemia. This case of acute lymphatic leukaemia was identified in a pharmaceutical worker who had a job considered dangerous because of high benzene exposure levels. Another worker at the same plant died of aplastic anaemia and the authors were of the opinion that some previous cases of aplastic anaemia reported in association with benzene exposure may also have been leukaemia. The company's means of dealing with the high exposure levels that caused these blood diseases was to rotate the workers out of the specific job every month.

4.2. Actions and inactions

4.2.1. Exposure recommendations

By 1939, the vast number of benzene poisonings among workers in all parts of the world led to the recommendation for the substitution of benzene with other solvents by a number of investigators (Greenburg, 1926; Erf and Rhoads, 1939; Mallory *et al.,* 1939). In 1939 Hunter, and Mallory *et al.,* reported 89 cases of 'poisoning' and three cases of leukaemia among workers exposed to benzene in a variety of occupations. Two of the 'poisonings' were associated with benzene levels of less than 25 ppm and 10 ppm, respectively.

Yet, in 1946, the American Conference of Governmental Industrial Hygienists (ACGIH) recommended a limit of 100 ppm for benzene exposure in the workplace (ACGIH, 1946). Subsequently, the recommended value was reduced to 50 ppm in 1947 and to 35 ppm in 1948 (ACGIH, 1948). Because of evidence of 'hypersusceptibility' to the bone marrow suppressing effects of benzene, a document published in 1948 by the American Petroleum Institute (API) concluded that the only absolutely safe level from exposure to benzene was zero (API, 1948). This opinion was based on observations of some workers developing various blood diseases indicative of bone marrow depression who had worked alongside other workers whose blood counts were in the normal range. The API then proceeded to recommend a limit of '50 ppm or less'. In 1957, the ACGIH lowered its recommended eight-hour time-weighted average exposure limit to 25 ppm for benzene (ACGIH, 1957).

4.2.2. Disregard for recommendations

In spite of the recommendations mentioned above, cases of aplastic anaemia, and central nervous system toxicity manifested by headache, nausea, giddiness, staggering gait, paralysis and unconsciousness (leading to death in 13 cases in the United Kingdom) continued to be reported in the 1940s and 1950s (Browning, 1965). These symptoms of the central nervous system are thought to be associated with benzene exposures ranging from 3 000 ppm to 20 000 ppm (Flury, 1928) — levels 200 to 800 times higher than the limits recommended in the 1940s and 1950s and 2 000 times higher than the 10 ppm level already associated with aplastic anaemia by Hunter and by Mallory *et al.* (1939).

In the 1950s and 1960s, an obvious lack of precaution for workers exposed to benzene was taking place in many parts of the world, including France, Italy, Russia, Turkey, the United Kingdom, the United States and other countries, as documented by the publication of case reports of blood diseases as a result of benzene exposures well above levels known to be toxic to the bone marrow and central nervous system of workers. For example, Vigliani and Saita, in 1964, reported that the risk of acute leukaemia among workers 'heavily exposed to benzene' in the rotogravure and shoe industries in the Italian provinces of Milano and Pavia was at least 20 times higher than for the general population. Vigliani (1976) reported that over 200 cases of benzene haemopathy, including 34 cases of acute leukaemia, had been treated at the Institutes of Milano and Pavia between 1942 and 1965. These workers were exposed to benzene levels ranging mostly from 200 to 500 ppm, with occasional peaks above these levels. In 1967, Goguel *et al.* reported 44 cases of benzene-induced leukaemia, mostly chronic forms, having occurred in the Paris region of France between 1950 and 1965.

Blood poisonings among workers exposed to benzene were being documented in other parts of Europe as well. As stated by Aksoy (1977), because 'benzene containing glue adhesives were extremely practical and cheaper in the market, they replaced their customary petroleum containing adhesives with the new product' in the shoe and slipper industry in Turkey in 1961. Benzene exposures experienced by these workers were reported to have been between 150 ppm and 650 ppm (Aksoy, 1978). By the mid-1970s, an epidemic of aplastic anaemia and leukaemia among Turkish shoe workers began to unfold as reported by Aksoy (Aksoy *et. al.*, 1971; Aksoy 1977 and 1978). The majority of the individuals who were identified in the reports from these European countries as dying from leukaemia as well as other benzene-related blood diseases were exposed to levels shown decades earlier to cause benzene poisoning. (For a review of case reports of benzene-related blood diseases associated with the countries mentioned above, see IARC, 1974.)

4.2.3. Epidemiological evidence for leukaemia

Beginning in the early 1970s, the University of North Carolina in the United States published a series of epidemiological studies demonstrating significant excesses of

leukaemia, mostly chronic forms, among workers exposed to presumably low atmospheric levels of benzene (McMichael *et al.,* 1975). The benzene exposure resulted primarily from the use of rubber solvents such as petroleum naphtha, toluene, mineral spirits, etc., that were contaminated with benzene ranging in volume from about 1–5 % in the 1940s to about 0.5 % for petroleum naphtha in the 1970s.

In 1977, Infante *et al.* published the results of the first cohort study of workers exposed specifically to benzene. The workers were engaged in the manufacture of a rubberised food wrap called Pliofilm. The study demonstrated a 5- to 10-fold risk of leukaemia among workers exposed to technical-grade benzene at levels that were generally considered within the various limits recommended over the time period 1940–1971, that is a 10 ppm time-weighted average to a maximum limit of 100 ppm (Infante *et al.,* 1977a). Until this time, benzene was considered a cause of leukaemia based not upon epidemiological studies, but rather upon case reports of leukaemia and the clinical observation that individuals with benzene-induced aplastic anaemia and other blood diseases transformed into acute leukaemia.

4.2.4. US attempt to control occupational exposure

In 1977, on the basis of the Infante *et al.* (1977a) study results supplemented by the world literature on benzene and leukaemia, the US Department of Labor (OSHA, 1977a) issued an emergency temporary standard (ETS) that would have reduced the occupational benzene exposure limit in workplace air to 1 ppm as an eight-hour time-weighted average. The 1 ppm exposure limit was based on the Occupational Health and Safety Administration's (OSHA's) policy at the time that exposure to carcinogens in the workplace should be lowered to the lowest feasible limit. Such feasibility analyses take into consideration both technological and economic feasibility.

The new OSHA ETS was stayed in 1977, however, in response to a challenge in the US Court of Appeals by the API, who in essence argued that there was no increased risk of developing leukaemia as a result of benzene exposures below the old limit of 10 ppm. Then OSHA proposed a permanent standard, requested comments and held a public hearing (OSHA, 1977b). In 1978, OSHA issued a final standard (OSHA, 1978) that included a 1 ppm atmospheric exposure limit. This standard was challenged by the API on the same grounds. The US Court of Appeals again vacated the final standard, and that decision was appealed to the Supreme Court. In an unrelated development, benzene was voluntarily withdrawn from consumer products in the United States after it was shown that use of a paint stripper in the home could generate atmospheric levels up to 200 ppm in a short period of time (Young *et al.,* 1978).

4.2.5. The US Benzene Decision and dose-response analyses

In July 1980, the US Supreme Court (IUD, 1980) issued what has become known as the Benzene Decision. This decision has had a major impact on OSHA's ability to control exposures to benzene and other toxic substances in the workplace. The court stated that before OSHA can promulgate any permanent health standard, the Secretary of Labor is required to make a threshold finding that a place of employment is unsafe in the sense that significant risks are present and can be eliminated, or lessened, by a change in practices. Although the Benzene Decision recognised the uncertainties involved, it indicated that the determination of 'significant risk' should, if at all possible, be established on the basis of an analysis of the best available evidence through such means as quantitative risk assessments. The Supreme Court in its general guidance for future OSHA rule-making noted that the requirement that a significant risk be identified is not a mathematical straitjacket and that it is the OSHA's responsibility to determine what it considers to be a significant risk based largely on policy considerations. In the only concrete example of significant risk, the court stated that if, for example, the odds are one in a million that a person will die from cancer by taking a drink of chlorinated water, the risk clearly could not be considered significant. On the other hand, if the odds are one in 1 000 that regular inhalation of gasoline vapours that are 2 % benzene will be fatal, a reasonable person might well consider the risk significant and take appropriate steps to decrease or eliminate it.

Since the Benzene Decision, OSHA has considered an occupational lifetime risk (over a 45-year period) of one extra case of cancer, or other material impairment of health consequence, per 1 000 workers to be

'significant'. It has not yet considered the other end of the range — what it considers to be a non-significant risk — because all the health standards that OSHA has promulgated since the Benzene Decision, with the exception of perhaps formaldehyde, have resulted in estimates of excess risk that are greater than one per 1 000 over an occupational lifetime. (For quantitative estimates of risk for health standards promulgated by OSHA since the Benzene Decision, see Infante, 1995b.)

A straightjacket, however, appropriately describes the risk analyses that OSHA currently engages in prior to proposing any regulatory action. The long delay recognised in OSHA promulgating standards before 1980 has now been superseded by additional detailed analyses of risk related to exposure. While on the surface such analyses may seem appropriate, they have become encumbered by additional analyses that take into account the mechanism by which the substances being regulated may cause cancer. Since the exact mechanism by which any substance causes cancer (including benzene which has been studied for decades) has not been identified, speculation and argument about various unproven hypotheses for cancer causation are time consuming. Many other issues also have been added to the debate on risk assessment procedures such as whether the mouse, the hamster, or the rat is the most appropriate species to use when human data are not available. Since the OSHA is required to review and comment on all possible cancer mechanisms, appropriateness of species, etc., the entire 'risk assessment' process has created additional years of delay in standard-setting. Instead of reasonable precautions being promulgated by government and employers, years pass as analyses are performed to determine the dose response between exposure and risk of disease. These analyses can also include incorporation of speculative mechanistic data that have not been validated.

4.2.6. Cost in lives of the prolonged regulatory process

Eleven years after the OSHA promulgation of an ETS for benzene, a new benzene standard that included a 1 ppm eight-hour time-weighted average exposure limit was finally issued (OSHA, 1987). The new limit was based on 'economic feasibility', not elimination of 'significant risk', as an occupational lifetime risk of 10 extra leukaemia deaths per 1 000 workers was associated with the 1 ppm limit. Other estimates of leukaemia risk, limited to the cohort data from the National Institute for Occupational Safety and Health (NIOSH) (as updated by Paxton *et al.,* 1994) and to deaths from acute myelogenous and monocytic leukaemias only, indicate a range of 0.02 to 5.1 per 1 000 excess deaths depending upon the estimates of benzene exposure and the model chosen (Crump, 1994). However, these later analyses are based on a follow-up period of the NIOSH cohort that results in selection bias for the reasons described below. Based on OSHA's final quantitative risk assessment for benzene and estimates of extra benzene exposure among the United States workforce during the 10 years that it took to complete the benzene standard, it has been estimated that an extra 198 deaths from leukaemia and 77 extra deaths from multiple myeloma will eventually develop among US workers as a result of the 10-year delay — deaths that could have been prevented (Infante and DiStasio, 1988). This estimate of preventable deaths from benzene exposure did not include blood diseases other than leukaemia, which were known at the time to be caused by benzene exposure, the reason being that there were no dose-response data available for the other blood diseases.

4.2.7. Expansion of lymphohaematopoietic diseases

The quantitative estimate of extra deaths from benzene exposure indicated above did not include non-Hodgkin's lymphoma, which has been shown more recently to be associated with occupational exposure to very low levels of benzene (Hayes *et al.,* 1997). Quantitative risk assessment (Infante, 1997) based on the 1996 Hayes *et al.* study results suggests an extra risk of 54 deaths from leukaemia/lymphoma per 1 000 workers exposed over an occupational lifetime (45 years). This risk is 54 times greater than a level considered significant by OSHA. The 1997 Hayes *et al.* study results and dose-response analyses based upon those data clearly demonstrate the inadequacy of the 1 ppm exposure limit for benzene based on cancer risk alone. Fortunately, most occupational settings in the United States are able to achieve benzene exposure levels in the range of 0.2–0.3 ppm, or lower. Additionally, the US standard includes provisions ancillary to the exposure limit such as exposure monitoring, medical surveillance and hazard training — all of which should presumably further reduce the

risk of benzene exposure and related diseases. In addition to quantitative risk assessment, direct observation of data from the 1997 Hayes *et al.* study demonstrates significantly elevated relative risks for all lymphohaematopoietic cancers combined, and for acute non-lymphocytic leukaemia and myelodysplastic syndrome combined, among the group of workers exposed to a constant average benzene level of only 1.2 ppm for 5.5 years for a total cumulative dose of 6.7 ppm-years (Hayes, pers. comm., 1999), which is a much lower cumulative dose than that allowed by a limit of 1 ppm over an occupational lifetime of 45 years (45 ppm-years of cumulative dose). Some individuals within the benzene cohorts who have died from leukaemia or lymphoma experienced estimated benzene exposures of 0.5–2 ppm for only 1–2 years or less (Infante, 1992).

By the 1990s, toxicologic research demonstrated the multiple-site carcinogenicity of benzene in experimental animals, and additional epidemiological studies and case reports of exposed workers expanded the carcinogenicity of benzene to all major forms of leukaemia in the aggregate (Savitz and Andrews, 1997; Infante, 1995a; Wong, 1987b) and specifically acute myelogenous leukaemia and its variants (Hayes *et al.,* 1997; Browning, 1965; Rinsky *et al.,* 1987; Bond *et al.,* 1986; DeCoufle *et al.,* 1983), acute lymphatic leukaemia (Hernberg *et al.,* 1966; Shu *et al.,* 1988), chronic lymphatic leukaemia (McMichael *et al.,* 1975;), chronic myelogenous leukaemia (Browning, 1965; Goguel *et al.,* 1967; Tareeff *et al.,* 1963; Infante, 1995a; Wong, 1987b;) and some minor forms such as hairy cell leukaemia (Aksoy, 1987; Flandrin and Collado, 1987), myelodysplastic syndrome (Hayes *et al.,* 1997), myeloproliferative disorders (Rawson *et al.,* 1941; Tondel *et al.,* 1995) as well as non-Hodgkin's lymphoma (Hayes *et al.,* 1997), including multiple myeloma (DeCoufle *et al.,* 1983; Rinsky *et al.,* 1987; Ireland *et al.,* 1997; Goldstein, 1990). An 'updated' analysis of the NIOSH benzene cohort (Infante *et al.,* 1977a; Rinsky *et al.,* 1987) by Wong (1995) concluded that the excess of multiple myeloma in the NIOSH cohort was no longer statistically significant. Wong (1995), however, changed the beginning date of follow-up from 1950 to 1940. In doing so, he introduced selection bias into his analysis because the company removed records for individuals who died at one of the study locations for several of the years prior to 1950. Thus, analyses of the NIOSH cohort by Wong (1995) that begin follow-up prior to 1950 cannot be relied upon for estimating risk of death from multiple myeloma, or any other cause of death.

4.3. Discussion

The response to information on the toxicity of benzene has at times demonstrated concern by some in the field of occupational health, particularly in the earlier years when large numbers of workers in various sectors and jobs were being surveyed to determine the extent of their blood diseases. Nevertheless, even during this period, benzene exposure levels were not reduced to levels commensurate with the toxicity data available at the time, and the epidemic of poisonings and leukaemia among benzene-exposed workers continued through the first six decades of the 20th century. Various reasons for the limited public health response and subsequent overexposure and disease in light of the knowledge of benzene toxicity are apparent.

4.3.1. Some reasons for lack of precaution

Lack of knowledge

The lack of precaution about exposure to benzene has been attributed in part to lack of knowledge of its toxicity during the first four decades of the 20th century. For example, even though Santessen (1897) reported four cases of aplastic anaemia among women manufacturing raincoats in Sweden in 1897, exposures were not lowered enough and Helmer (1944) reported 60 cases of benzene poisoning (58 were women) at a single raincoat manufacturing facility in the same country in 1940 and 1941. The epidemic of benzene poisoning in Sweden was ascribed in part to a lack of knowledge of the toxicity of benzene by plant management and workers (Helmer, 1944).

Cost of solvents

Several investigators who surveyed workforces and identified workers with various benzene-induced blood diseases, namely Greenburg and colleagues in 1926, Erf and Rhoads in 1939 and Mallory *et al.* in 1939, recommended the substitution of benzene with other solvents. Yet, worldwide consumption of benzene in the marketplace continued to expand after the Second World War. One of the reasons for expanded use of benzene in the synthetic rubber industry is that it was such a good rubber solvent. Another reason, as expressed by Aksoy

(1977), is that benzene was cheaper than other solvents used in the shoe and slipper industry in Turkey. Thus, economic consequences led to other solvents being replaced with benzene in the Turkish shoe manufacturing industry as late as 1961. This substitution with benzene led to high-level workplace atmospheric benzene concentrations and to the epidemic of leukaemia, preleukaemia, pancytopenia and other blood diseases as reported by Aksoy (Aksoy *et al.*, 1971; Aksoy, 1977 and 1978). Thus, economic considerations in the 1960s (Aksoy, 1977) further contributed to the overexposure and subsequent benzene-related diseases.

Consensus recommendations and corporate influence

The 1939 reports by Hunter and Mallory *et al.* indicated that some cases of benzene poisoning were associated with levels of 25 ppm and 10 ppm. Yet, in 1946, the ACGIH recommended a limit of 100 ppm. Although the ACGIH recommendation for benzene was lowered to 35 ppm in 1948, this level was still higher than the levels reported in association with benzene poisonings. From my personal experience over the years, it is apparent that one of the problems being faced in the occupational health community for benzene (as well as for other toxic substances) is that consensus organisations usually base their recommended exposure levels on what is easily achievable in the workplace. Data related to level of exposure and toxicity are reviewed, but are not translated into health-based exposure-limit recommendations. Castleman and Ziem (1988) investigated this behaviour by the ACGIH and concluded that the ACGIH threshold limit values (TLVs) were based heavily on corporate influence. Thus, consensus recommendations were inadequate and corporate influence may have played a role in these recommendations and in the resultant proliferation of benzene-induced diseases in the workplace. Castleman and Ziem (1988) were of the opinion that an international effort was needed 'to develop scientifically based guidelines to replace TLVs in a climate of openness and without manipulation by invested interests'. To date, this goal has not been achieved (Castleman and Ziem, 1994).

Anti public health attitude (call for scientific certainty)

In the 1970s, benzene manufacturers and users began a new approach for conveying knowledge about the toxicity of benzene to the public in general, and to workers and plant managers specifically, which contributed to a continuation of overexposure to benzene. This is the period when manufacturers began to hire consultants to downplay the importance of the scientific observations related to the toxicity of benzene and to introduce unresolvable arguments about dose-response analyses, which had an impact in delaying much needed government regulations that sought to reduce benzene exposure in the workplace. Economic considerations were again being given a higher priority than concerns for public health, but this time the economic concerns appeared to be based on the cost of lowering exposures (OSHA, 1987), and perhaps on the increasing cost of litigation and liability related to workers contracting benzene-related diseases on the job. This era has fostered the development of arguments that seek to minimise or misrepresent study results. In my opinion, it is part of a new anti public health approach that calls for scientific certainty in terms of causality for every specific lymphohaematopoietic disease related to benzene by exposure level. As a result, workers employed worldwide in benzene exposure operations today may not be afforded the appropriate protection to the extent feasible in order to reduce their risk of haematopoietic diseases and many of those who develop benzene-related diseases may receive little or no compensation.

For example, during the OSHA rule-making hearings held in 1977, it was argued that the benzene cohort study conducted by NIOSH, which demonstrated a 5- to 10-fold elevated risk of leukaemia (Infante *et al.,* 1977a), was meaningless in terms of public health intervention to reduce exposures in the workplace. Although not persuasive, one of the arguments raised by consultants to the industry was that the study had simply identified a random leukaemia cluster, and since clusters of leukaemia are known to occur in time and space, this cluster of leukaemia just happened to be identified among a cohort of benzene-exposed workers (Tabershaw and Lamm, 1977). (See Tabershaw and Lamm, 1977, and Infante *et al.*, 1977b, for a series of arguments and rebuttal of the study findings.) It was further argued that benzene could not cause leukaemia in workers because there was no evidence that benzene caused cancer in experimental animals (Olson, 1977). This

argument was clearly fictitious given the overwhelming evidence of carcinogenicity provided by the study of humans. In any case, shortly thereafter the evidence of carcinogenicity of benzene in experimental animals became available (Maltoni and Scarnato, 1979; NTP, 1986).

In the 1980s, when OSHA again published a new benzene proposal taking into consideration the guidance offered by the Supreme Court's Benzene Decision on determination of the significance of health risk, attention during the rule-making focused on the dose-response analyses prepared by OSHA and its consultants in support of its new standard (OSHA, 1987). Most of the argument addressed the benzene exposure assessment portion of the risk assessment, with new estimates of exposure among the benzene cohort members being provided for time periods in which there were no exposure data available. These 'educated' guesses by the various parties involved in the rule-making could not be confirmed. Proposed government regulation of benzene, however, resulted in a number of new dose-response analyses and a protracted debate about which exposure assessment was the most appropriate for use in the quantitative risk assessment — the resolution of which can never be determined with scientific certainty. Argument about the type of dose-response model that was most appropriate for benzene exposure and risk of leukaemia was also raised. While nobody would object to debate on these issues, the continuation of the arguments for protracted periods of time resulted in workers and the public in general being unnecessarily exposed to benzene levels that could have otherwise been reduced through a shorter regulatory process. Studying a subject to death often results in the death of those we are trying to protect (Infante, 1987).

In the 1990s, the US National Cancer Institute (NCI), in collaboration with the Chinese Academy of Preventive Medicine (CAPM), published a series of ongoing studies of Chinese workers exposed to benzene. These studies (Hayes *et al.,* 1997 and 1996; Dosemeci *et al.,* 1996) demonstrate a dose response for exposure to benzene and leukaemia, lymphoma, myelodysplastic syndrome and aplastic anaemia. They also demonstrate, through direct observation, high relative risks for leukaemia, myelodysplastic syndrome and non-Hodgkin's lymphoma as a result of very low average benzene exposures, such as around 1 ppm. Since the results of these well-conducted studies may be used in the future by governments in Europe, the United States and other countries for estimating benzene-related diseases from low-level exposure to the general population, the findings have broad implications for public health intervention. In response to the publication of these studies, consultants to the chemical industry have published critiques of both the health findings and the benzene exposure estimates related to those findings (Wong, 1998 and 1999; Budinsky *et al.,* 1999), which in the opinion of some misrepresent the data on health effects as well as the benzene exposure estimates made by the NCI/CAPM investigators (Hayes *et al.,* 1998; Hayes, pers. comm.). Some of these same consultants have also expressed surprising views about the more general findings related to benzene exposure and disease (Wong, 1995 and 1996; Bergsagel *et al.,* 1999). For example, based on his analysis of data from the NIOSH benzene cohort study, one author concluded that benzene can only cause acute myelogenous leukaemia, in contrast to other types of leukaemia, and that the threshold is between 370 and 530 ppm-years of exposure (Wong, 1995). In this publication, he failed to include data from his own benzene study whereby he reported a statistically significant dose response for benzene exposure and leukaemia among workers whose cumulative benzene exposures ranged from less than 15 ppm-years to more than 60 ppm-years (Wong, 1987a and b). Furthermore, in the latter study, none of the leukaemia deaths were from acute myelogenous leukaemia. Thus, the findings and conclusions he drew from his own study contradict his opinion that benzene causes only acute myelogenous leukaemia and that the cumulative exposure threshold is between 370 and 530 ppm-years.

Wong (1995) further concluded that there is no evidence that benzene exposure was associated with multiple myeloma in the NIOSH study because he could not identify a dose response based on four cases of multiple myeloma in the study population. Lack of ability to observe a dose-response relationship based on four deaths from multiple myeloma is essentially meaningless, because four cases are too few to allow enough statistical power to observe a dose response if in fact one were present. In any case, Rinsky *et al.* (1987) of NIOSH had previously demonstrated a significant excess of death from multiple myeloma among the

benzene cohort members and concluded that low-level benzene exposure was related to multiple myeloma. Wong (1995) has also argued that benzene in general is not associated with multiple myeloma and, contrary to the findings in the NCI/CAPM study, he has argued that there is no evidence that benzene is associated with non-Hodgkin's lymphoma (Wong, 1998) — conclusions that appear to be at odds with the views of others on benzene toxicity (Goldstein and Shalat, 2000; Goldstein, 1990; Rinsky *et al.,* 1987; DeCoufle *et al.,* 1983; Infante, 1995a; Savitz and Andrews, 1996 and 1997; Hayes *et al.*, 1998 and 2001).

The arguments about the NCI/CAPM study seem reminiscent of the protracted debate and delay in necessary government action that took place after release of the NIOSH benzene study in 1977 (Infante *et al.,* 1977a). It will be unfortunate if more precaution is taken with the use of data from the NCI/CAPM study than with the protection of populations exposed to levels of benzene that can be reduced with technology currently available. Scientific certainty is difficult to achieve, but stressing the uncertainty does not do justice to the data on benzene exposure and related diseases. In the case of benzene historically, taking precaution to maintain exposure levels in the workplace in accordance with the scientific data available at the time would have eliminated much needless suffering and death among the workers. In my opinion, the protracted argument about the dose response for benzene-related diseases among exposed workers and denial about the lymphohaematopoietic diseases most likely associated with benzene exposure is counterproductive to efforts to provide a workplace relatively free of harm. While the continuation of this debate may be interesting from an academic viewpoint, it also raises the question of whether it may be more a reflection of economic concerns and potential liability on the part of companies than a concern for the public's health based on a reasonable interpretation of available scientific data.

4.3.2. Benzene in gasoline a continuing hazard

Most consumers and many medical personnel are not aware of the fact that gasoline contains benzene. In the United States, gasoline has contained an average of about 1.5 % benzene for the past two decades, but may reach 5 % by volume (Infante *et al.,* 1990). Historically, petrol in most European countries has contained more benzene than US varieties and the trend apparently still existed through 1994 (Deschamps, 1995), but the benzene content has supposedly been reduced more recently. Not surprisingly, epidemiological studies, analyses and case reports have demonstrated an association between gasoline exposure and leukaemia (Schwartz, 1987; Jakobsson *et al.,* 1993; Infante *et al.,* 1990), other blood diseases (Infante *et al.,* 1990; Lumley *et al.,* 1990; Naizi and Fleming, 1989), chromosomal defects (Lumley *et al.,* 1990; Hogstedt *et al.,* 1991) and other manifestations of genetic damage (Nilsson *et al.,* 1996). Yet, gasoline station pumps do not provide adequate information on the cancers known to be associated with benzene exposure. Nor do the material safety data sheets for gasoline provide the available evidence on chromosomal or genetic damage.

Because of this lack of candour about the hazards of benzene in gasoline, garage mechanics and highway maintenance workers take unnecessary risks by using gasoline as a solvent in cleaning auto parts (Infante, 1993), and consumers take unnecessary risks by using gasoline as a solvent and fail to take the necessary precautions when using gasoline in various home appliances such as lawn mowers, weed trimming devices, power saws, etc. In addition, a study of roadside vendors who sold re-packaged gasoline in Nigeria has demonstrated that 26 % had neutropenia as compared to 2–10 % in controls, a significant difference (Naizi and Fleming, 1989). The hazards of benzene in gasoline have been recognised since at least 1928, when Askey (1928) reported a case of aplastic anaemia in a US worker exposed to gasoline, and more recently by the report of a case of myelofibrosis in a Swedish petrol station attendant (Tondel *et al.,* 1995) and a case of aplastic anaemia in a US roofer who used petrol to clean seams before fitting rubberised roofing material (Infante *et al.,* 1990). Despite the overwhelming literature on the hazards of benzene in petrol, the public health community and safety officials, including those employed by industry, have yet to come to grips with the task of adequately informing workers and consumers about this hazard.

4.4. Conclusions and lessons for the future

The available knowledge on the toxicity of benzene and the failure to take precautions to protect workers (and the public in general) in light of this knowledge over the past century is cause for concern. The inaction or inadequate actions by consensus organisations and governments alike throw into question the ability of these organisations to protect the health of the public. In the case of benzene exposure in the workplace, the precautionary principle is not relevant. Recommendations made in the United States and the United Kingdom in the 1920s for the substitution of benzene with other solvents known to be less toxic to bone marrow went unheeded for decades even though high percentages of workers being surveyed demonstrated blood disorders. Furthermore, benzene was not withdrawn from consumer products in the United States until 1978 and this was done by manufacturers on a voluntary basis, and it has never been adequately validated.

It is also difficult to accept the claimed ignorance of the toxicity of benzene in the raincoat manufacturing industry in Sweden in the 1940s when 60 cases of blood poisoning in a single factory were reported. Forty years earlier (in 1897) published case reports of aplastic anaemia among women employed in this same industry in Sweden appeared in the literature. The claim that management was unaware of the hazards of benzene exposure in such a small industry in a country known for its humanitarian concerns is incomprehensible. In the 1940s and 1950s, 13 deaths from the neurotoxic effects of benzene were reported to have occurred in the United Kingdom. The benzene exposure levels associated with these acute deaths were most likely more than 200 to 800 times the occupational exposure levels recommended at the time. Clearly, this situation could, and should, have been avoided had there been any serious concern for worker health.

With the knowledge available at the time, it is also difficult to understand how benzene was substituted for other petroleum solvents in the shoe industry in Turkey in 1961. Aksoy states that the substitution was made because benzene was cheaper than the other solvents. Data on the costs of benzene and the other solvents in Turkey in the 1960s are not available, but it is unlikely that the difference could have been more than a few cents a gallon. Yet, the epidemic of leukaemia and other fatal blood diseases that followed this substitution had to have been very costly in terms of the workers' diseases, the associated expenses for health care and the loss of wages, etc. This is simply a case, as in other instances, of the cost of production being more important to the manufacturers than the cost of human life.

Even though numerous case reports (in the thousands) of benzene-related blood diseases, including leukaemia, were reported in the literature, precautionary measures to reduce exposure levels below those known, or reasonably anticipated, to cause blood diseases were not taken, and recommended exposure limits by consensus organisations like the ACGIH were based on those that were easily achievable in the workplace. According to Castleman and Zeim, such recommendations stemmed from the participation of scientists employed by various corporations on the Threshold Limit Value Committee that made the exposure recommendations. Thus, one of the lessons to be learned, if not already obvious, is that consensus organisations in the process of developing exposure limits for chemicals should maintain distance from the producers of the chemicals and their 'consultants' when evaluating evidence for the diseases of concern.

Finally, affixing a warning label on gasoline pumps that includes the cancers and other diseases known, or likely to be caused by benzene exposure, may serve to reduce unnecessary benzene exposure to garage mechanics, petrol service station attendants, highway maintenance workers and consumers who fill their own gas tanks, but who more unknowingly use the gasoline in consumer products at home, and not infrequently use gasoline as a solvent at home without full knowledge of its cancer and non-cancer disease risks. Failure adequately to inform the public of the cancers, bone marrow proliferative diseases and genetic hazards associated with benzene in gasoline is to repeat our failures of the 20th century in the 21st century and to make a mockery of public health education.

Benzene: early warnings and actions — Table 4.1.

1897	Santessen report on observed aplastic anaemia in Sweden and other reports show that benzene is a powerful bone marrow poison
1926	Greenburg and colleagues observe abnormally low white blood cell counts in benzene workers
1928	Dolore and Borgomano publish the first case of benzene-induced leukaemia
1939	A number of investigators recommend the substitution of benzene with other solvents, but this was not implemented
1946	American Conference of Governmental Industrial Hygienists (ACGIH) recommends a limit of 100 ppm for benzene exposure, even though some cases of benzene poisoning were associated with levels of 25 ppm and 10 ppm
1947	Recommended value reduced to 50 ppm
1948	Further reduced to 35 ppm
1948	American Petroleum Institute (API) concludes that the only absolutely safe level is zero, but recommends 50 ppm or less
1957	ACGIH lowers recommended exposure to 25 ppm
1950s-60s	Obvious lack of precaution for workers exposed to benzene in many parts of the world with fatal consequences
1977	Infante *et al.* publish the first cohort study of workers linking benzene exposure directly to leukaemia
1977	Based on these results, the US Department of Labor wants to reduce exposure to 1 ppm, but is challenged in the courts by API
1978	Benzene was voluntarily withdrawn from consumer products in the United States
1980	US Supreme Court issues the Benzene Decision severely limiting regulatory actions
1987	New benzene standard of 1 ppm. This 10-year delay caused more than 200 deaths in the United States
1996	Studies showing benzene-related diseases from 1 ppm level of exposure
2001	Petrol contains benzene, giving public exposure risk

Source: EEA

4.5. References

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