

NIOSH Revised Recommendation for an Occupational Exposure Standard for Benzene

The National Institute for Occupational Safety and Health (NIOSH) recommended on August 25, 1976 that occupational exposure be controlled so that no worker will be exposed to benzene in excess of 1 ppm (3.2 mg/m³) in air as determined by a 2-hour air sample collected at 1 liter per minute. Previously, in a criteria document transmitted July 24, 1974, to the Occupational Safety and Health Administration (OSHA) in the Department of Labor, NIOSH recommended adherence to the present Federal standard of 10 ppm as a time-weighted average with a ceiling of 25 ppm (but without the permitted excursion to 50 ppm as in the existing standard). At that time, NIOSH, recognizing that there were data suggesting a relationship between exposure to benzene and the occurrence of leukemia and other malignant diseases among employees at risk of such exposure, expressed the need for detailed, comprehensive epidemiologic investigations of the long-term relationships of morbidity and mortality due to leukemia and other malignancies in the population at large and that of workers with benzene. The recommendation for a more stringent standard was made after review of evidence subsequently accumulated from clinical as well as additional epidemiological data indicating that benzene is leukemogenic. Because it causes progressive malignant disease of the blood-forming organs, NIOSH recommends that for regulatory purposes, benzene shall be considered to be carcinogenic in man.

An issue of particular concern is the presence of benzene in gasoline and its impact, particularly in gasoline station operations. Recent information indicated that service station attendant exposures were less than 10 ppm total gasoline vapors and that if United States gasolines remain at about 1 percent by volume of benzene, exposure levels to ben-

zene will probably stay below 1 ppm. Future efforts to reduce evaporative losses at gasoline stations under EPA regulations should help to further decrease exposure to benzene at such facilities. Emphasis should be placed on prohibiting the occupational use of benzene as a solvent or diluent in open-type operations. Furthermore, product substitution should be a paramount consideration wherever benzene is identified or its presence suspected, especially with concurrent indications of alterations in the blood or the hematopoietic system, it should be replaced with less harmful substitutes wherever feasible.

Because it is not possible at present to establish a safe exposure level for a carcinogen, the NIOSH recommendation is to restrict exposure to very low levels that can still be reliably measured in the workplace. The NIOSH recommendation can be expected, at a minimum, to materially reduce the risk of benzene-induced leukemia. The recommended standard is readily measurable by techniques that are valid, reproducible, and available to industry and Government agencies.

In addition to possibly causing leukemia, exposure to benzene can result in central nervous system depression and skin irritation. Compliance with all sections of the NIOSH recommended standard should prevent noncarcinogenic adverse effects of inhalation or dermal exposure to benzene in the workplace. NIOSH estimates that 2 million workers are potentially exposed to benzene in printing, lithography, and dry cleaning, and in the manufacture of coke and gas, adhesives, coatings, and a variety of chemicals. The proposed standard would apply to the processing, manufacture, and use of benzene and benzene products covered by the Occupational Safety and Health Act.



U.S. DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE
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UPDATE CRITERIA AND RECOMMENDATIONS FOR A REVISED BENZENE STANDARD AUGUST 1976

In 1974, the National Institute for Occupational Safety and Health (NIOSH) issued criteria and recommendations for a standard for occupational exposure to benzene [1]. A cause-and-effect relationship between benzene and observed blood abnormalities, especially aplastic anemia, was recognized. At that time, NIOSH, recognizing that there were data suggesting a relationship between exposure to benzene and the occurrence of leukemia among employees at risk of such exposure, expressed its need for detailed comprehensive epidemiologic investigations of the long-term relationships of morbidity and mortality due to leukemia and other malignancies in the population at large and in those who work with benzene.

Between 1974 and mid-1976, seven epidemiologic studies have been reported [2-8] along with case reports of benzene-related blood dyscrasias [9-11] and chromosomal aberrations [11-14]. Although some investigators have observed only acute forms of benzene-associated leukemias [9-12], a recent connection with chronic leukemias has been noted [3,4,13]. Reports prior to 1974 of chronic myelocytic or lymphocytic leukemia [15-18] and erythroleukemia [19-23] are not as numerous as the observations of acute myelocytic or lymphocytic types [16,17,24-26]. Because of the rarity of erythroleukemia, Vigliani and Forni [12] regard as significant the three cases which they have observed. Because case records accumulated by one investigative group [12] of patients with acute or subacute leukemia have become so numerous in the past two decades, many cases formerly diagnosed as acute pancytopenia are now considered to be examples of acute leukemia.

In 1974, McMichael et al [3] reported on the first phase of a study of a population at risk comprised of active and retired employees

of a major tire-manufacturing plant in Akron, Ohio. A cohort of 6,678 male rubber workers was followed for 9 years (1964 through 1972), and data on 1,783 deaths were obtained. Comparison with the 1968 US national mortality data yielded a Standardized Mortality Ratio (SMR) in the U.S. male population of 99 from all causes of death for the full cohort and of 93 for an active employment subcohort in the age range of 40 to 64. Among other findings of cause-specific deaths, the highest SMR's were for deaths from causes related to the hematopoietic and lymphatic systems. The SMR showed an excess mortality of approximately 2-2.5 and was higher for the "active" age range (40-64) than for the full age range (40-84). For leukemia deaths in the 40-64 age range, the SMR was 315—approximately a threefold excess. It was recognized that, because no distinction was made in this evaluation between different groups of workers having different work experiences, a "dilution effect" could occur. A second phase of the study [4,6] compared different groups of rubber workers. McMichael et al [3] stated that, from this initial study alone, it should not be assumed that the observed cause-specific mortality excesses were attributable to work-environment exposure within the rubber industry. Such excesses could have been a spurious association such as a "selected" population in which all persons living in Akron might have been exposed to some specific unknown factor. Similar findings from 5 other plants in widely differing parts of the US, however, make this explanation unlikely, in the opinion of the authors. Pending completion of the second phase of the study, the authors concluded that they could only suspect, rather than conclude with confidence, that working in certain jobs within the rubber industry entails an increased risk of dying from these specific causes.

In a followup of the same cohort [3], Mc-

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Michael et al [4] in 1975 extended the epidemiologic study to indicate an association between leukemia and jobs entailing exposure to solvents among which benzene was once the solvent of choice. After noting that leukemias in general demonstrated a threefold excess in mortality in the 40-64 age range, and with further subclassification of the International Classification of Diseases categories to identify specific leukemias, a sevenfold excess of deaths from lymphatic leukemia in the 40-64 age range was observed. Six of eight deaths were from chronic lymphatic leukemia. Myeloid leukemia was the next highest category in this age range, showing a twofold excess. At smaller plants not located in Akron, Ohio, a complete study was not performed for reasons of cost and time; nevertheless, a proportional mortality analysis demonstrated a 45% excess of leukemia. The question of whether the observed mortality excesses were associated with specific job categories within the rubber industry was then investigated. Nineteen of 70 occupational titles were associated with solvent exposure and were grouped as heavy, medium, and light solvent exposure. A discriminant function analysis based on time spent in various work groups and independent of the previously observed mortality excess revealed a statistically significant positive association between solvent exposure and lymphatic leukemia. One job title within the 3 solvent-exposure groups, tire repair, showed a sixfold difference between cases and controls in a comparative test of relative risk of lymphatic leukemia. It was pointed out that tire repair involves considerable swabbing of tires with solvent, and, at some time in the past, the solvent predominantly used was benzene. Because each of the 4 cases observed had started working at the plant at some time since 1945, it was suggested that the leukemogenic agent may be a chemical that had been present in recent decades and may still be present. Finally, it was of interest to the authors [4] that it was lymphatic rather than myeloid leukemia that appeared to be associated with solvent-exposure jobs.

A third study by McMichael et al [6] in 1976 involving the same cohort of rubber workers previously reported [3,4] indicated

that mortality from lymphatic leukemia was also very strongly associated with working in the synthetic plant, a place where NIOSH has been unable to identify benzene-related exposures. The synthetic plant is essentially a chemical plant making important synthetic-rubber intermediate products, such as styrene-butadiene and neoprene. An unexpected association of lymphatic leukemia with the janitoring-trucking occupational title group was explained by speculating that the transfer of workers to this group occurred for medical reasons, especially where conditions were not rapidly fatal and for which active employment could be maintained while in apparent disease remission or stabilization. Andjelkovic et al [5], studying the same cohort as McMichael et al [3,4,6], distinguished between active worker mortality experience and retired worker mortality experience, particularly in workers who retired before age 65. Results were essentially the same as previously reported [3,4,6] with findings of excess mortality for both active and retired workers from neoplasms of the lymphatic and hematopoietic tissues. In addition, the expectation was confirmed that workers who retired prior to the normal retirement age of 65 would have a less favorable mortality [experience] than active workers of the same age range; however, the magnitude of the excess, an SMR of 202 as compared with 61 for the active workers, was unexpected (p less than 0.001).

Monson and Nakano [7] in 1976 reported another mortality study in a cohort of 13,571 white male rubber workers, again in Akron, Ohio. From the records of 5,079 deceased employees, excess deaths from leukemia occurred most often among workers in the tire (18 observed/11.7 expected) and in the processing (10/4.2) divisions. Excesses were also seen among workers in the chemical division (2/0.7), in elevator areas and cleaning (3/0.4), in shops (7/6.6), and in industrial products (9/7.0). Benzene was reported to have been used extensively in the industry. While pure benzene was no longer used as a solvent, it was stated to be a contaminant in many of the solvents still used [7].

In a mortality study of 20,163 petroleum-

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refinery workers carried out in 17 refineries [8], mortality from lymphomas was reported to be greater than expected, though not statistically significant, in 3 categorized exposure groups listed as high exposure (laboratory, maintenance, and salvage-recovery jobs), low exposure (plant security, utility, purchasing, and motor transport jobs), and medium exposure (all other jobs). A suggestion was made of increased mortality with increased exposure. No mention was made of benzene exposure. In an epidemiologic survey of leukemia reported by Thorpe [2] in workers in a variety of petroleum and petrochemical operations, a number of problems of data collection were experienced. The incidence of benzene-associated leukemia was not considered to be abnormal compared to that of the general population in the countries concerned. Emphasis was placed on the need for improvement in the recording and storage of biologic observations, job histories, occupational exposures, and demographic data.

A 1971 report by Ishimaru et al [27] deserves to be mentioned here because it specifically associates benzene or its derivatives and medical X-rays with an approximately 2.5 times excess risk of leukemia in workers. Ishimaru et al [27] organized 15 groupings based on occupational categories reportedly listed by Milby et al [28] as workers who handle benzene or are exposed to medical X-rays. Four categories were not included in the reported results because the authors found no leukemia in either test or control workers with such occupational histories as lithographers, painters, and laboratory technicians; yet, these workers might well be expected to experience benzene exposure because of the known presence of benzene in such occupations. Many of the selected occupations such as carbon dioxide-gas furnace workers, tinsmiths, sheetmetal workers, soft drink-manufacturing workers, and barbers were not listed by Milby et al; furthermore, those occupations would not likely have benzene exposure. In addition, no investigation was made of the specific chemical agents handled by the individuals engaged in the selected occupations and the identified cases of leukemia in both the test and the control groups were generally

low, mostly numbering only 1 or 2. Occupations where a high association with benzene exposure would be expected, such as leather products workers and workers engaged in printing, repairing, or cleaning of printing machines, showed no excess whereas welders, platers, tinsmiths, or sheetmetal workers demonstrated an excess of leukemia where extensive use of benzene would be questionable. This study [27] is not considered to be sufficiently definitive to conclude that a relative risk of leukemia from probable occupational exposure to benzene or its derivatives exists.

Animal experiments designed to investigate the carcinogenic action of benzene have failed to give reliable information on its capacity to produce an increased incidence of leukemias [29]. Lignac [30] in 1932 claimed to have produced six cases of leukemia and two cases of lymphosarcoma in a strain of white mice given 0.001 ml benzene in olive oil once a week by subcutaneous injection for up to 11 months. Attempts to repeat these observations have yielded equivocal results [31-34]. A high tumor incidence often manifested as leukemias in untreated mice has been found to be caused by certain virus strains. It has therefore been considered quite conceivable that leukemias described in the earlier experiments in mice after benzene treatment have, in large part, developed spontaneously or by virus infection, rather than being caused by benzene [29].

The literature is replete with medical case reports of leukemia directly associated with occupational exposure to benzene. These leukemias have occurred throughout the industrial world, most frequently as a result of using benzene in solvent applications. In France, Goguel et al [17] in 1967 described 50 instances of leukemia, of which six had already been reported, in the Paris region from 1950 to 1965. The 44 new cases included 13 chronic myelocytic leukemias, 8 chronic lymphocytic leukemias, and 23 acute leukemias. Frequent disturbances of the erythrocytes and their precursors were noted. Girard and Revol [16] added four observations of acute myeloid leukemia and nine cases of chronic lymphocytic leukemia in 1970. In the Soviet Union,

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Tareeff et al [18] found 6 acute and 10 chronic cases of leukemia among what were described as printers, primers, apparatus men, and chemists. In papers published mostly through the 1970's, Aksoy and coworkers [9,10,24, 35-39] in Turkey have identified more than 50 patients with aplastic anemia and 34 cases of leukemia, all in workers having chronic exposure to benzene. These included one case of erythrocytic leukemia, three cases having a possible genetic predisposition, and one case of chronic myelocytic leukemia. In addition, a suggested relationship between Hodgkin's disease and chronic benzene exposure was reported. In Italy, 34 fatal cases of benzene-associated aplastic anemia and leukemia have been observed [12]. Data from the Institute of Occupational Health of Pavia, Italy, indicate that, of 16 deaths occurring between 1960 and 1974 among 142 workers identified with chronic benzene poisoning, only 3 died of aplastic anemia and 13 died of leukemia [12]. The observations of at least 20 cases of acute erythroleukemia in the literature is considered to be significant [12] because of the rarity of the disease. Vigliani and Saita [40] in 1964 calculated that, for workers heavily exposed to benzene in the provinces of Milan and Pavia, the risk of acute leukemia was at least 20 times that of the general adult population. Cases of benzene-associated leukemia have also been reported in Spain [20], Scandinavia [22], and the United States [13,25].

The consistent observations of chromosomal aberrations associated with benzene exposure continue to be reported [13,41,42]. The implications of the chromosome findings with respect to benzene leukemia are still not clear. The possibility of a chromosomal instability acting as a stimulus for a latent leukemogenic virus has been speculated upon [12].

The recently reported isolation of a complete human RNA tumor virus (Type C) associated with acute myelocytic leukemia [43,44] raises again the possibility that a chemical carcinogen activates a latent leukemogenic virus in accord with the generalized suggestion of Todaro and Huebner [45]. The demonstration of a relation between exposure to ben-

zene, the appearance of a virus in exposed human beings, and the occurrence of acute leukemia in these people would strongly support such a hypothesis.

It is apparent from the literature that so-called benzene leukemia continues to be reported. The inadequacies in correlating exposure-effect relationships were discussed by NIOSH in 1974 [1] and studies subsequent to 1974 which would aid in evaluating the consequences of exposures to various airborne concentrations of benzene have not been found in the literature. Case records of patients with acute or subacute leukemia have become so numerous that, according to Vigliani and Forni [12], they exceed those of acute pancytopenia, a fact which has led to the belief that many cases previously considered as pancytopenia may indeed have been examples of hemocytoblastic leukopenic and aleukemic leukemia. In spite of the diversity of chemicals to which workers are frequently exposed, both singly and in mixtures, the development of blood abnormalities can, for the most part, be linked with exposures to benzene. Data are lacking to support the suggestion by Girard and Revol [16] that homologues of benzene might be leukemogenic. Vigliani and Forni [12] observed that since the replacement of benzene with toluene as a solvent in the rotogravure industry in 1964, no new cases of aplastic anemia or of leukemia due to toluene exposure have been seen. Furthermore, workers have not shown the chromosome aberrations frequently seen in workers exposed to benzene. The statement by Gerarde [46] that benzene is unique among hydrocarbons in its myelotoxic potency seems as valid today as in 1960 when it was made. The excess risk of leukemia recently reported in the rubber industry by separate investigative groups [3-7] is considered by NIOSH to be indicative of probable benzene exposure, especially since benzene was at one time the agent of choice for many solvent operations.

NIOSH considers the accumulated evidence from clinical as well as from epidemiologic data to be conclusive at this time that benzene is leukemogenic. Because it causes progressive, malignant disease of the blood-

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forming organs, NIOSH recommends that, for regulatory purposes, benzene be considered carcinogenic in man. In view of this conclusion and since it is not possible at this time to establish an exposure level at which benzene may be regarded to be without danger, NIOSH recommends that exposure to benzene be kept as low as possible. The use of benzene as a solvent or diluent in open operations should be prohibited. Furthermore, product substitution should be a paramount consideration. Wherever benzene is identified or its presence suspected, especially with concurrent indications of alterations in the blood or the hematopoietic system, it should be replaced with less harmful substitutes wherever feasible.

The sampling and analytical method for benzene in air recommended by NIOSH [1] employs adsorption on charcoal followed by desorption and gas chromatographic measurement. Personal sampling pumps operating at approximately 1 liter/minute, for a 10-minute sample at a mean concentration of 22.8 ppm, collected a quantity of benzene that, upon analysis, yielded a relative standard deviation (precision) of 11.6% [1]. Results from collaborative testing indicate that sampling at 1 liter/minute for 2 hours will collect a sufficient quantity of benzene from an airborne concentrations of 1 ppm to allow a relative standard deviation in the range of that previously reported [1], which is considered acceptable. One ppm represents the lowest level at which a reliable estimate of occupational exposure to benzene can be determined at this time, in consideration of the limitations of biologic and air measurement techniques. NIOSH recommends that occupational exposure be controlled so that no worker will be exposed to benzene in excess of 1 ppm (3.2 mg/cubic meter) in air as determined by an air sample collected at 1 liter/minute for 2 hours.

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