BENZENE IN FLORIDA GROUNDWATER - AN ASSESSMENT OF THE SIGNIFICANCE TO HUMAN HEALTH

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HUMAN HEALTH EFFECTS OF BENZENE

Introduction

Benzene has long been identified as a hazardous toxic agent. Both acute and chronic effects from high exposure may be severe, but there is considerable debate about the minimum level of safe exposure. The present report is a review of literature concerning reported human health effects of benzene. Both acute and chronic toxicity are covered. With respect to the latter, hematologic, cytogenetic and other potential hazards are identified. Whenever possible, the group of persons included in the study are described as well as the documented exposure assessment.

Acute Toxicity

Acute accidental benzene poisoning has occurred both at work and in the home. Additionally, intentional benzene poisoning has been reported as a result of "glue-sniffing" among adolescents.

Early symptoms of benzene toxicity include irritation of the conjunctiva and respiratory tract, malaise, nausea, vomiting, headache, and the feeling of exhilaration (Drozd and Bockowski, 1967). Benzene is lipid soluble. It is pharmacologically classed as an anesthetic although it is no longer used because of its therapeutic index (Winek and Collom, 1971). If exposure is severe, a deep anesthesia may be produced with resultant narcosis, coma and death from respiratory arrest. It has also been suggested (Von Oettinger, 1952) that severe, acute benzene poisoning may result in direct myocardial damage.

Gerarde (1960) sought to estimate the levels of exposure associated with particular benzene effects. It was noted that 19,000 to 20,000 parts per million (ppm) for 5 to 10 minutes would be fatal; 7500 ppm for 30 minutes would be dangerous to life; 1500 ppm for 60 minutes would produce serious symptoms; 500 ppm for 60 minutes would produce symptoms of acute poisoning; 50-150 ppm for 5 hours would produce headache, malaise and weakness; 25 ppm for 8 hours would have no effect. The National Academy of Science (1976) indicated that exposure at the level of 25,000 ppm would be rapidly fatal. Snyder (1984) emphasized that mild central nervous system effects appear to be rapidly reversible following cessation of exposure, that there is no evidence that these effects result in chronic brain damage, and that the effects appear to be concentration dependent since lower levels of benzene do not seem to elicit severe responses no matter how long the individual is exposed.

A. Hematotoxicity

Nearly ninety years have passed since Santesson reported, in 1897, that 9 persons using benzene in the production of bicycle tires developed aplastic anemia. The first report associating leukemia with benzene exposure occurred in 1928 (Delore and Borgomano). As noted by Goldstein (1977) a major problem in understanding human hematotoxicity to benzene is that exposure has usually occurred to a mixture of volatile compounds, rather than to benzene alone. On the other hand, the association between hematopoietic disorders and benzene exposure has been relatively strong, there has been an apparent lack of similar association with other known volatile agents in comparable occupational settings, outbreaks of hematotoxicity seem to have been abated in industries where benzene has been replaced, the association has been reproduced in many occupational and non-occupational exposures throughout the world, and toxicity in animal studies has been shown to produce bone marrow effects when benzene has been the sole experimental agent. Today, the primary questions concerning hematotoxicity concern the smallest amount of benzene which is required to produce an adverse effect.

Aplastic Anemia/Pancytopenia.

Pancytopenia may be defined as a decrease in circulating erythrocytes, granulocytes, and platelets. In very severe cases, the decrease in these three blood cell counts is accompanied by a corresponding decrease or absence of their precursors within the bone marrow, and a diagnosis of aplastic anemia is made. Just as aplastic anemia may represent a highly severe portion of continuum of changes which may affect the bone marrow due to benzene toxicity, unicellular cytopenias may represent less severe forms of a pancytopenic effect.

Table 1 presents a review of 72 reports, dating from 1897 to the present, which deal with benzene associated pancytopenia and aplastic anemia. The table outlines the number of cases involved, whether or not an occupational association was found, the nature of the occupational and/or non-occupational exposure, and the exposure assessment technique which was used.

Nearly all of the reports deal with occupational exposures. Among those reports for which exposure assessment methods are available, qualitative associations or a general indication of the number of years of exposure dominate, particularly prior to 1965. Among the investigations in which a case of aplastic anemia or pancytopenia was detected, the lowest absolute level of benzene reported is 15 ppm (Kliche, 1969). Workers in this study, however, were on the job for an average of 17 years. A somewhat lower minimum level of exposure, 11 ppm, was found by Goldwater and his colleagues (Goldwater, 1941; Goldwater and Tewksbury, 1941; and Greenberg, et al., 1939), in their evaluation of over 300 rotogravure printers in New York. There, a change in the printing process had led to the exposure of workers at levels of benzene ranging from 11 to 1060 ppm for periods ranging from six months to three years. Significant cytopenias were found among 23 of the workers, and six required hospitalization.

As noted by Snyder (1984), these studies are particularly convincing with respect to a causal relationship between benzene and pancytopenia due to the many different work settings and different countries involved where the only common thread appears to have been benzene. Additionally, the studies of Aksoy, et al. in Turkey (1971, 1972, and 1976), temporal relationship between the use of benzene and the outbreak of hematologic toxicity in leather workers was established. Specifically, in 1971, 51 of 217 apparently healthy workers were found have hematologic problems, including six workers with pancytopenia. The exposure in these cases was estimated to have been from 30 to 210 ppm of benzene, for three months to 17 years. In 1972, Aksoy's group cited 32 cases of significant aplastic anemia in workers exposed to benzene for four months to 15 years at exposure levels ranging from 150 to 650 ppm.

While tending to support the causal nature of an association between benzene and pancytopenia, however, neither the positive reports discussed above nor the negative ones (notably those of Shima, 1975; Townsend, 1978; and Pagnatto, 1979) have been able to establish a lower level of exposure below which cytopenic effects are not observed. A more direct approach to this question has been taken by Doskin (1971) and Chang (1972). These studies were described in detail by the Environmental Protection Agency (1978), and were summarized by Snyder (1984). In Snyder's summary, it is noted that many details as to exposure are not given in either of these two studies. Specifically, Doskin (1971), working in the Soviet Union, studied 365 workers who had three years of exposure in a new chemical factory. Serial hematologic studies were done on exposed workers as well as a control group. Benzene exposure levels are expressed in terms of the maximum allowable concentration, 5 ppm. Benzene exposure exceeded this level by two to eight fold in 64% of the measurements during the first year of the factory's operation, 37% in the second year, and 3% in the third year. The decrease in benzene levels was paralleled by the decline in the number of workers with hematologic abnormalities. It was concluded that exposure of workers to concentrations of 10 to 40 ppm of benzene for less than one year may produce mild cytopenic effects. Detailed information concerning the benzene monitoring system which was used and the actual levels of benzene recorded, however, were not documented in the report.

Chang (1972) studied 119 workers exposed to benzene in an unspecified Korean worksite. Twenty-eight of these workers experienced hematologic problems, including 21 with anemia, 2 with leukopenia, and 5 with both. A graph was presented which plotted each of the affected individuals in terms of duration of work (on the abscissa) and level of benzene exposure (on the ordinate). Based on this plot, an exponential function was obtained which implied a "threshhold" of 10.0 ppm for cytopenic effects. However, among the 18 workers exposed to 10 to 20 ppm of benzene in the study, no hematologic toxicity was observed. As noted by Snyder (1984) a major problem in understanding this study is the lack of information about the definition of work exposure confidence concentrations for individual employees.

B. Leukemia

As is true for pancytopenia, the association of benzene with leukemia has a long history. Summarization of this history has been complicated by the fact that hematologists differ in how they define leukemia subtypes. There are differences not only in terms of the evolution of criteria over time, but also because standards differ in different countries. Nosology is particularly important in leukemia because there are major differences between the various subtypes in terms of the frequency of occurrence, the clinical course, the prognosis, and possibly the etiologic mechanism. In summarizing the literature for the present report, the classification as developed by Goldstein (1977) is used. Leukemia is defined as a neoplastic disease with increased numbers of white cell or white cell precursors in the blood or bone marrow. Leukemias are usually subdivided depending on whether they are acute or chronic and in terms of the cell type involved. Acute myologenous leukemia is the commonest form of adult leukemia, and is the form of this disease that has been most frequently related to benzene. In this disease, there is a proliferation of cells which are morphologically related to the normal myeloblast, which is the precursor of granulocytic blood cells. There are several variants of acute myeloblast leukemia, the one most frequently reported in association with benzene being erythroleukemia. Acute myelomonocytic leukemia, in which the precursor is a myeloblast which has the morphological appearance of a monocyte, and acute promyelocytic leukemia, morphologically a somewhat more mature leukemic cell, have also been associated with benzene, but to a lesser extent. True monocytic leukemias are rare, but have also been associated with benzene exposure. Another uncommon form of acute leukemia, usually called stem cell leukemia, is defined by proliferation of very immature bone marrow precursor cells.

Chronic myelogenous leukemia and possibly related diseases, including essential thrombocythemia, myelofibrosis with myeloid metaplasia are often lumped together under the heading of myeloproliferative syndrome. This reflects their presumed origin in the same precursor cell. Controversy persists, however, concerning the relationship of these disorders to each other.

Lymphocytic leukemias are also classified as acute and chronic. Acute lymphoblastic leukemias is the commonest form of childhood leukemia. Chronic lymphocytic leukemia usually occurs in late adult life where it is often slowly progressive and not a cause of death.

Studies relating benzene exposure to leukemia are summarized in Table II. As noted by Snyder (1984), the support that these case reports give to the idea of a causal relationship between benzene and leukemia is only partly due to the number of cases involved. With respect to acute myeloblastic leukemia, the relatively common finding of a worker with aplastic anemia associated with benzene exposure who passes through a preleukemic phase into frank acute leukemia (Aksoy, et al., 1972; 1976; Girard and Ravol, 1970; Mallein, et al., 1971; and Tareef, et al., 1963) is especially impressive. It is also of note (Snyder, 1984) that there is a relatively high frequency of association between

erythroleukemia and benzene exposure since this is a relatively rare variant of acute myelogenous leukemia. As was true with respect to pancytopenia and aplastic anemia, further support for the association between benzene and leukemia is provided by the diverse occupational and geographical settings from which these reports originate. Despite the diversity, benzene seems to be the common thread.

As regards chronic myelogenous leukemia and its possibly related disorders including essential thrombocythemia and myelofibrosis with myeloid metaplasia, there are scattered case reports in the literature, but they form a less impressive body of evidence than the group of studies relating benzene exposure to acute myelogenous leukemia.

There are only a few scattered reports relating acute lymphoblastic leukemia to benzene. The same is generally true for chronic lymphocytic leukemia. The strongest support for an association between benzene and chronic myelogenous and/or chronic lymphoid leukemia comes from France. Specifically, Goguel, et al., (1966, 1967) reported 50 cases of leukemia in benzene workers near Paris between 1960 and 1965. Among the 44 new cases in this group there were 13 with chronic myelogenous leukemia, 8 with chronic lymphoid leukemia. The relatively high proportion of these types of leukemia, however, have not been replicated in other case series.

While case reports and case series' can provide circumstantial evidence of an association between an exposure of interest (in this case benzene) and a particular disease, such investigations cannot provide a scientific test of the hypothesis that the exposure of interest is associated with increased risk of the disease. Such hypothesis testing is in the realm of analytic epidemiology. Such studies have been done among shoemakers in Istanbul, in the rubber industry, in the printing industry and in the petroleum and petro-chemical industry. Additionally, a case control study has been done among patients with blood diseases in a hospital in Lyon, France. In general, while these studies tended to support the idea that exposure to benzene is causally related to the occurrence of leukemia, many of the investigations have been severely criticized. Controversy has been particularly strong regarding the low limits of benzene exposure which may be associated with the development of leukemia. A specific discussion of these studies follows.

Aksoy and coworkers reported on leukemia among workers in small shoemakeing shops in Istanbul. Between 1955 and 1960, a solvent with high levels of benzene was introduced into the Turkish shoe industry. The first cases of aplastic anemia were observed in these workers in 1961, and leukemia appeared in 1967 (Snyder, 1984). Between 1967 and 1975 among 28,500 shoemakers in Istanbul, the estimated incidence of leukemia was estimated to be 13 per 100,000 per year in contrast to the incidence in the general population which was estimated to be 6 per 100,000. The concentration of benzene in the air of the workrooms of the shoemakers was estimated to be 150 ppm, and the exposure had lasted from four months to 17 years (Aksoy and Erdem, 1969). Benzene was banned as a solvent in 1969, and the incidence of

leukemia, after peaking in 1973 decreased in 1974 and 1975. No cases were reported in 1976, 1977, or 1978 (van Raalte and Grasso, 1982).

Snyder (1984) noted several methodologic shortcomings in Aksoy's work. Specifically, Snyder pointed out that the definition of occupation used for workers with leukemia differed from that used for the official records. It was possible that a worker with leukemia was called a shoe worker whereas the same person appeared on the official record as having another occupation. Additionally, there was no follow-up of the 28,500 workers exposed to benzene, and it was possible that some cases of leukemia were missed. Further, the stated incidence rate of 6 per 100,000 per year for the general population was for an unknown location and an unknown time, and no age standardization was done in making the comparison between the incidence rate for the general population and that for the shoe workers. Finally, the exposure levels reported by Aksoy and co-workers represented occasional random measurements taken in what was in essence a cottage industry.

Several cohorts of rubber workers have been studied including investigations Pagnotto et al. (1961, 1979); McMichael et al. (1974, 1975, 1976); Andjelkovic et al. (1976, 1978); Monson and Nakano (1976); and Infante et al. (1977). These investigations have been summarized and critically reviewed by van Raalte and Grasso (1982). In their review van Raalte and Grasso note that Pagnotto et al. (1961) performed a survey in a rubber coating industry where a benzene worker had died from panmyelophthisis. In a follow-up study 18 years later (Pagnotto et al. 1979), 38 workers who were exposed for one to 24 years at a level of 10 to 50 ppm (PWA) with short term peaks which were higher, there was no occurrence of either blood dyscrasia or leukemia. In the study by McMichael et al. (1974) a three-fold excess mortality from leukemia was found. Though the workers exposed to solvent had a seven-fold excess of death from lymphatic leukemia with six of eight deaths resulting from chronic lymphatic leukemia. In contrast, only a two-fold excess mortality was detected for myeloid leukemia. Subsequent studies by this group confirmed the excess risk of leukemia among solvent exposed workers. An historic-prospective study in a cohort of rubber workers over the period 1964 through 1973 was done by Andjelkovic et al. (1976). While increased risks for neoplasms of the hematicpoietic and lymphatic systems were found for white males, white females did not experience excess mortality. Wolf et al. (1981) were noted to have performed a case control study involving 72 workers with leukemia which had occurred between 1964 and 1973 in four rubber and tire companies with moderate levels of benzene exposure. While increased risk for lymphatic leukemia was identified, no increased risk was detected for myelogenous leukemia. Monson and colleagues (1976, 1981) reported on mortality among 29,087 men and women who had worked in a rubber plant at least two years within the periods from 1940 through 1974 and 1974 through 1978 respectively. In both instances an excess mortality from leukemia was found.

Van Raalte and Grasso were particularly critical of the studies performed by Infante and co-workers in the rubber industry. In 1977,

Infante et al. reported a five-fold increase of all leukemia and a ten-fold in the combined incidence of myeloid and monocytic leukemias. It was stated that 'the benzene levels themselves were generally below the limits recommended at the time of their measurements,' (referring to threshold limit values in force at the time exposure 100 ppm in 1941 to 10 ppm in 1971) and that exposure levels from 1969 onward were, 'in most instances ranging from 0 to 10 or 15 ppm' (van Raalte and Grasso, 1982). This statement appeared to be contradicted by Infante (1977) during OSHA benzene hearings in November and December of 1977. Specifically, at the hearings it was indicated that the leukemia cases were more probably related to unknown but apparently quite high levels (in excess of 100 ppm) of benzene exposure.

In 1981, Rinsky et al. published a followup to Infante's 1977 report. The identical cohort was used in the followup study but it was based upon 98% vital status identification of the study group versus 75% in the 1977 report. There were seven deaths due to leukemia among 748 workers who had at least one day of exposure to benzene between 1940 and 1950. The leukemia cell types involved were myelocytic or monocytic. In contrast, to the seven cases identified in the followup study comparable United States death rates standardized for age, sex, and calendar time period were expected to yield only 1.25 leukemia deaths. This Standardized Mortality Ratio (SMR) is equal to 560, $p < 0.001$. The mean duration of benzene exposure in the conort was less than one year. For workers exposed to benzene for five or more years leukemia deaths produced and SMR of 2,100. Four additional cases were excluded from the analyses. These included a 67 year old man with a latency for acute myelogenous leukemia of 37 years, an individual who was among salaried employees not in the original cohort, an individual with acute lymphocytic or aleukemic leukemia and an individual who was diagnosed by a hematologist as having acute myelocytic leukemia but whose death certificate listed the cause as aplastic anemia.

While Snyder (1984) felt that Rinsky's investigation indicated that benzene is a human carcinogen at levels not greatly above the current legal standard, van Raalte and Grasso (1982) advanced an argument which reached the opposite conclusion. Specifically, van Raalte and Grasso noted that one of the cases in Rinsky's group of seven was a worker with chronic myelogenous leukemia which had developed after only one month of exposure to benzene. This is at variance with most clinical experience and suggested that other factors besides benzene may have been involved. Additionally, all cases included in Rinsky's group of seven occurred between 1950 and 1961, and the only exception among the total of 12 cases identified was that worker for whom the period of latency was 37 years. Further, van Raalte and Grasso pointed out that there were no new cases at all in employees who were first exposed after 1951. On the contrary, the period of exposure for all cases started in the first 13 years since the plants opened, that is from 1937 through 1950. Moreover, with the exception of the aforementioned unusual case of chronic leukemia with only one month of exposure, the two cases with the most recent onset had the shortest latency period, three and one-half and four years respectively. In other words, patients exposed to higher concentrations of benzene have

a longer latency. This, they argue is inconsistent with both general clinical experience and experimental precedent. Finally, all of the cases in Rinsky's primary set of seven had a latency period of less than 22 years. Since the plant closed in 1976, there were only two possible (or suspect) cases noted in 26 years of employee exposure between 1950 and 1976 plus five subsequent years of followup, through 1981. Even granting these two cases, van Raalte and Grasso feel that Rinsky's data shows a decline in the incidence of leukemia which parallels the decline in benzene exposure at the factory's in question. Far from indicating an association between leukemia and low level exposure to benzene, van Raalte and Grasso suggest that Rinsky's data is more consistent with the interpretation that low levels of benzene exposure show no excess in leukemia mortality.

Turning to studies in the printing industry, Lloyd, et al. (1977) found an increase in the number of deaths from leukemia among printing pressmen, eight observed versus 5.1 expected. Green, et al. (1979) performed a cancer mortality among male U.S. Government Printing Office employees who had worked during the period January 1948 through April 1977. A significantly higher proportion of deaths were related to multiple myeloma, leukemia, and Hodgkin's disease. Although the excess leukemia deaths occurred primarily in binder's whose benzene exposure was ended in the early 1960s, there was little or no change in leukemia mortality after the discontinuance of benzene. As such, the low level exposures to benzene may not have been associated with an excess incidence of leukemia (van Raalte and Grasso, 1982).

Paganini, et al. (1980) performed a mortality study in Los Angeles of 1,361 web pressmen with one or more years of exposure during the period 1949 through 1965. Seven cases of leukemia were observed versus 2.8 expected in a comparable U.S. white male population. Six of the seven cases were of the myelomonocytic type. Additionally, myelogenous leukemia was mentioned in a secondary role in one case and another man had myelofibrosis (van Raalte and Grasso, 1982).

As regards the petrochemical industry, Ott, et al. (1978) and Townsend, et al. (1978) performed a mortality study of 594 workers involved in three production areas on or after January 1, 1940 through January 1, 1974. Because of limited information available regarding the work place exposure assessment was limited to data collected between 1953 and 1972. During this time the time weighted average exposure to benzene was estimated to be generally less than 10 ppm although some exposures in excess of 30 ppm occurred including occasional higher values with a peak of 937 ppm. Among all workers studied, there were 102 deaths versus 128.2 expected on the basis of age-time specific rates for white males in the United States. There were two deaths from leukemia while 1.0 was expected. A third death occurred and was attributed to pneumonia although the individual had acute myeloblastic leukemia. Both van Raalte and Grasso (1982) and Snyder (1984) point to the relatively small size of this study population in suggesting that the data are insufficient to provide a reliable and independent estimate of the relationship between benzene and the risk of developing leukemia.

In addition to the mortality studies, Townsend, et al. (1978) performed a health examination study among 282 workers from this cohort. There was no indication of adverse benzene effects in this group.

Another investigation, by Thorpe (1974), involved a much larger population, 38,000 persons employed or on pension from a large oil company during the period from 1962 through 1974. Over a ten year period, 18 cases of leukemia were recorded versus an expected value of 23.2. Precise statements of exposure levels to benzene were unavailable. Several other investigations in the petrochemical industry include studies by Theniant and Goulet (1979), Hanis, et al. (1979), Thomas, et al. (1980) and Rushton and Alderson (1980, 1981). In only one case was an excess of deaths associated with leukemia demonstrated. Theniant and Goulet (1979) studied the mortality of 1,205 men employed for more than five years in a Canadian oil refinery in East Montreal between 1928 and 1976. Three deaths from leukemia and lymphoma were identified from death certificates versus 2.36 expected. Hanis, et al. (1979) studied employees of Imperial Oil Company exposed to petroleum products during 1964 to 1973. The mortality of the exposed group was compared with that of a non-exposed group concerning cancer of the lymphatic and hematopoietic systems seven deaths were identified in the exposed group and 15 in the non-exposed group. Thomas, et al. (1980) studied 3,105 union members in Texas who worked from 1947 through 1977. Although the study was small, an increased relative frequency of leukemia and multiple myeloma was demonstrated among white males with more than ten years of membership. Rushton and Alderson (1980, 1981) studied 35,000 workers with more than one year of service at eight oil refineries in the United Kingdom between January 1950 and October 1975. There were 30 cases of leukemia identified, but this was relatively less than would have been expected in comparison with national rates. Additionally, these authors formed a case control study on the same population using two sets of refinery controls per case. One set of controls was matched for refinery and year of birth while the other was also matched for length of service. Industrial hygienists classified exposure as low, medium or high. In no case was a statistically significant association demonstrated between benzene exposure and leukemia, although the risk of medium plus high exposure workers taken together relative to the risk of those with low exposure approached statistical significance at the level of $p = 0.05$ (van Raalte and Grasso, 1982).

C. Other Hematologic Diseases.

In addition to pancytopenia/aplastic anemia and leukemia, several other hematologic problems have been associated with benzene. At present, however, the associations have been noted only at the level of case reports and case series. Aksoy (1975) reported a case of paroxysmal nocturnal hemaglobinuria in a 74 year old male with a ten year of benzene exposure in a dye factory. An additional case is noted in this paper but the details are not given. Croizat, et al. (1948) also has reported a case of paroxysmal nocturnal hemaglobinuria associated with benzene poisoning. This disorder is of interest despite the fact that the case reports relating the problem of benzene exposure are relatively few. Patients with paroxysmal nocturnal hemaglobinuria often develop acute leukemia, and during the course of leukemic disorders red cell characteristics consistent with paroxysmal nocturnal hemaglobinuria may occur. This suggests that paroxysmal nocturnal hemaglobinuria is a paraneoplastic disorder (Goldstein, 1977).

Several investigations have linked benzene exposure to the occurrence of lymphomas, including Hodgkin's disease. The largest series was reported by Aksoy in 1974. Among 94 patients admitted with Hodgkin's disease to their clinic in approximately five years, six had a history of occupational exposure to benzene. The results of this study, however, are difficult to interpret. For example, as pointed by the authors themselves, the incidence of Hodgkin's disease in the general population was unknown as was the population at risk to benzene exposure. As such, it was impossible to estimate the relative incidence rates for Hodgkin's disease among people with and without benzene exposure.

CYCTOLOGIC AND CYTOGENIC EFFECTS

Investigations concerned with the effects of benzene on replication at the cellular level have focused on changes in cell nuclei, DNA metabolism, cell division and chromosome alterations; these all constitute direct measures of changes in the quantity, structure, organization, or function of cellular DNA, and the changes are both heritable and in many instances, imply continuing and/or progressive changes of the genome (Wolman, 1977). As is true with respect to hematologic effects, investigations as to the cytologic and cytogenic effects of benzene comprise both case reports and epidemiologic studies. Several of the case reports have described additional chromosomes. In two instances this chromosome was identified as a member of the C group. However, in both instances the patients involved were experiencing acute leukemia, and an additional C group chromosome is frequently found in this disease whether or not benzene is associated. Additional abnormalities noted in the case reports include tetraploidy and polyploidy (Wolman, 1977).

With respect to epidemiologic studies, several of the more recent investigations have been critically summarized by Snyder and Laskin (1985). These investigators note that Tough and Court-Brown (1965) reported on chromosome aberrations in peripheral blood lymphocytes from 20 workers having from one to 20 years benzene exposure. While exposed workers showed an increase in lymphocytes with both unstable and stable chromosome aberrations the difference was not statistically significant in terms of controls. This paper, however, was but a preliminary communication for a followup study which appeared in 1969. The second report deals again with the 20 subjects in the 1965 paper whose exposure consisted of leaks from a closed distilling operation. An additional 12 workers, whose exposure was from open vats of benzene, were also included in this report. Durations of exposure ranged from one to 25 years. At the time the cytogenic analyses were done, between two and six years had elapsed since cessation of exposure due to the substitution of toluene in the vat operation. In the distillation operation, however, exposures were ongoing. In this study, peripheral lymphocytes with unstable aberrations were significantly increased among the first group of 20 subjects. This was true in comparison with both onsite and general population controls. The second group of 12 subjects showed increased unstable aberrations when compared with the general population but not when compared with controls from the benzene free areas of the factory. Snyder and Laskin (1985) note several problems of interpretation with this investigation. There is, they state, an apparent failure to consider the potential confounding factor of age. There was a significant correlation between age and the number of aberrant cells but no correlation between years of exposure to benzene and numbers of unstable chromosome aberations. Moreover, the data were not considered to be adequate to assess the nature of the relationship between benzene exposures and the number of unstable chromosome aberations. Additionally, hematological data were not presented. Finally, in addition to age, other potential confounding factors were excluded from consideration by the authors, the single exception being exposure to ionizing radiation.

Forni et al. (1971a) studied 32 workers with a history of benzene related clinical disease and from 1 to 18 years benzene exposure. When compared with age-sex matched controls, the exposed workers had a statistically significant increase in the proportion of peripheral lymphocytes with both stable and unstable lymphocytes. Potential confounding due to exposure from other cytotoxic agents (e.g. smoking, drugs) was not addressed in these analyses, however, (Snyder and Laskin, 1985).

In a separate study reviewed by Snyder and Laskin (1985), Forni et al. (1971b) were noted to have investigated workers who, prior to 1953, experienced benzene hemopathy while working in a rotogravure plant in which measured airborne concentration ranged from 131 to 532 parts per million. Toluene was substituted for benzene in 1953, and subsequent toluene exposure were about 200 parts per million. In 1967-68, 34 workers, including 10 with the pre-1953 benzene exposure, had cytogenetic studies on 100 cultured lymphocyte metaphases. Healthy, unexposed age-sex matched controls were also studied. Exclusion criteria removed persons with recent viral illness or vaccinations from study entry. Two persons exposed to therapeutic irradiation and three with other chemical exposures were not included in the analyses. Benzene exposed workers (eight of whom had experienced hemopathy including two with severe disease) had significantly more unstable chromosome changes (1.66% versus 0.6%), $p < 0.01$), significantly more calculated breaks (1.8% versus 0.67%) and significantly more stable changes (0.62% versus 0.09%) than controls. Exclusion from the analysis of the two workers with severe hemopathy did not substantially alter the conclusions. Benzene exposed workers also had significantly more aberrations than workers exposed only to toluene. No correlation was observed between frequency of chromosomal change and either age or length of benzene exposure. Notably, three workers, each having three years of benzene exposure and a history of mild anemia and/or leucopenia, were cytogenetically normal. Additionally, two other workers, one with seven and one with 22 years of benzene exposure, had no history of hemopathy but did have 2 to 4 % abnormal cells. In summary, this is an important study which lends substance to the circumstantial evidence, provided by case reports, that high-level benzene exposure is causally associated with cytogenetic damage on a population basis. So far as individuals are concerned, however, the study also demonstrates present inability to ascribe a particular adverse effect to a particular level of exposure. Factors accounting for individual variability remain to be delineated.

Picciano (1979) compared 52 workers having one month to 26 years of benzene exposure with 44 pre-employment controls whose average age was 12.7 years less than the exposed group (Snyder and Laskin, 1985). The TWA exposure per workers was 2.1 parts per million over the four year period prior to study, but the documentation is not clear regarding duration of individual exposure, peak exposure, or potentially confounding factors such as smoking, recent illness, or the presence of other environmental clastogens (Snyder and Laskin, 1985). Overall, benzene exposed workers had a ten-fold excess in the proportion of

individuals with either chromosome breaks or markers. Snyder and Laskin (1985) also note a comment by Dabney (1981) as to the unusually low frequency of aberrations in controls for the Picciano (1977) study, a factor which may have affected the apparent significance of the results.

Van Raalte and Grasso (1982) have also criticized the Picciano study. Like Snyder and Laskin (1985) they criticize the exposure assessment. They also point out a large difference in age between exposed workers and controls (mean of 39 and 27 years respectively). Additionally, they note that while there were statistically significant differences in the frequencies of some chromosomal aberrations, the overall frequencies were low enough to have been considered normal in both groups.

Finally, Snyder and Laskin (1985) comment on a 1984 report by Sarto, et al. (1984) in which blood lymphocytes from 22 health, benzene, toluene and xylene exposed workers were compared with lymphocytes from a metallurgic factory. The benzene exposed group experienced levels of 0.2 to 12.4 ppm TWA in 1980-81, but pre-1971 exposures were markedly higher. The average duration of benzene exposure ($\pm$ standard deviation) was 11.4 $\pm$ 7.0 years. The study groups were matched for absence of other genotoxic exposure, medical history, smoking and eating habits, recent viral infection, number of x-rays in the preceding five years, drug consumption, and incidence of familiarl spontaneous abortions and malformations. Chromosomal aberrations were signficantly higher in benzene exposed (1.1%) than in control subjects (0.5%0, even when gaps were eliminated from consideration. Sister chromatid exchanges were detected with similar frequencies in both study groups.

D. OTHER POTENTIAL EFFECTS

While human benzene toxicity has been most often investigated in terms of adverse hematologic, carcinogenic and cytogenic effects, there are many suggestions in the literature as to other potential hazards. These are summarized in Table III and include adverse reproductive outcome; cardiovascular, renal, neurological, psychological, immunologic, ophthalmologic, and gastro-intestinal effects; injection injury; and Goodpasture syndrome. As is true for the more heavily investigated problems, these observations have generally been made in occupational settings. Evidence concerning these potential problems, however, is not so well developed as it is for hematologic and cytogenic effects. Much of the work remains to be replicated and hypothesis testing investigations are not always available.

SUMMARY

Based on human studies Benzene may have both acute and chronic effects on health. Acute Benzene exposures below 25 ppm for 8 hours do not seem to produce symptoms. Concentrations of 50 - 150 ppm for five hours may produce acute headache, malaise, and weakness. Very high concentrations (in the range of 25,000 ppm) may be fatal.

Of greater concern are chronic effects. These have been reported almost exclusively among the occupationally exposed. Hazards include cytogenetic damage, hematologic cytopenias and leukemia. The effects of occupational exposure, however, are not uniform across individuals, and as shown in a key study of cytotoxicity (Forni, et al., 1971b), factors mediating individual response are not well delineated.

The minimum level which may produce adverse effects among the occupationally exposed is controversial. For example, one of the strongest pieces of evidence cited concerning danger from low levels comes from the investigation of leukemia in rubber workers (Rinsky, et al., 1981). The identical data, however, was interpreted by Van Raalte and Grasso (1982) to indicate that low levels of benzene are not associated with excess risk.

Additional potential hazards are currently being investigated. These include other cancer, adverse reproductive effects, electroencephalographic changes, cardiovascular effects, immunologic and psychological effects, and Goodpasture syndroms. Some of these effects are noted only in case reports. Others reflect initial hypothesis testing efforts.

TABLE I.

PANCYTOPENIA / APLASTIC ANEMIA

year	reference	first author	number of cases	type of manufacture	non-occupational exposure	exposure assessment
1897	69	Santesson	9	bicycle tires	-	qualitative
1910	71	Selling	3	tire/rubber cameras, shoes	-	qualitative
1934	11	Anderson	1	-	amateur photography; home repairs, inc. paint removal	5 years
1938	30	Emile-Weil	27	cartriges chemical	4 children affected	<2 to >5 yrs.
1938	77	Undritz	1	cartons	-	5 years
1939	19	Bowditch		varied	-	100 to 350 ppm
"	45	Hunter	40			
1939	55	Mallory	14	rubber, leather telephone	painter's son developed leukemia	6 months-12 years
1939	39	Greenburg		printing	-	11 to 1,060 ppm
1941	37	Goldwater	0*			6 mo. to 3 yrs.
1942	23	Chevalier	3	perfume	-	15 to 26 yrs.
1942	28	Duvoir	2	raincoats, cars	-	qualitative
1942	78	Wilson	23	rubber	-	Avg.=100 ppm; max=500ppm
1943	25	Davidson	1	bookbinder	-	6 yrs.(leukemia)
1944	41	Hamilton-Patterson	50 (neutropenia) 44 (leucopenia)	rubber	-	
1946	42	Helmer	60	rubber	-	137 to > 218ppm
1965	16	Binet	1	synthetic leather	-	blood benxene
1946	16	Bernard	212	aeronautics		ogr 4 to 3 gr 3per m
1946	29	Duvoir	2		-	ogr 2 per kg of marrow
1947	128	Hutchings	87	aeronautics	-	50 to 530 ppm/day
1948	58	Oldfelt	37	printing, rubber	-	qualitative
1950	18	Blaney	2	plastics	-	qualitative
1951	12	Andre	1	hunting clothes	-	qualitayive
1954	68	Saita	17		-	qualitative
1956	21	Cassan	18	electrical appliances	-	qualitative
1956	70	Salvilahti	107	shoes	-	10 yrs., 400 ppm
1957	13	Appuhn	6	"	-	"
1959	34	Gadrat	"	"	-	8
1959	38	Gorini	5		-	qualitative
1960	56	McLean	6	petrol(10% Benzene) siphoned by mouth (3) walked through area with pools of petrol (1% benzene)(1) washed car parts(1) accidentally swallowed (1)	-	3 times/week for 8 weeks 4 months, 7 months 12 months 2 years 1 occasion
1961	14	Barrelet	3	varied		case 1: 3 yrs. case 3: 13 years
1961	127	Dubois	3	watch dial		70-400 ppm

TABLE 1. continued

year	reference	first author	number of cases	type of manufacture	non-occupational exposure	exposure assessment
1962	24	Curletto	3	raincoats, leather	-	18 months, 3 yrs., 16 yrs.
1962	53	Ludwig	2	chemical		14 and 19 yrs.
1963	26	Degowin	1	housepainter	-	13 years
1963	35	Gallinelli	3	worked with a glue diluted in benzene (60%)	-	3, 12 and 16 yrs.
1963	52	Lob	6	"	-	~35 ppm
1964	62	Pollini	14	"	-	"
1965	20	Browning	1	chromatographic testing of coal gas	-	qualitative
1965	63	Powars	1	-	glue sniffing	3 years
1965	47	Jindrichova	1	cobbler	-	46 yrs worked with 20-26% benzene paste
1966	7	Aksoy	3	various small shops and factories	-	6 months to 11 yrs.
1966	43	Hernberg	58	shoes	-	Salvilahti (1956)
1967	75	Stewart	10	chemicals	-	chronic=<25ppm acute=85 to 115 ppm for 3 months
1969	49	Kliche	13	roof tilers	-	average= 17 yrs. 15 ppm
1969	50	Koslova	"	leatherette	-	"
1964	111	Pollini	5	"	-	"
1969	64	Ralyevic	1	"		"
1970	36	Girard	-	varied	-	10 to 25 ppm
1970	67	Roth*	-	shoes	-	
1971	8	Aksoy	6	shoes	-	30 to 210 ppm 3 months to 17 years
1971	27	Doskin	152	chemicals	-	benzene exceeded mpc by 2-8 times in 64% of samples in yr. 1, 37% in yr. 2, 3% in yr. 3
1971	33	Forni	17	varied	-	qualitative
1971	40	Guberan	5	watchmaking	-	qualitative
1971	54	Mallein	2	chemicals	-	"
1972	9	Askoy	32	varied	-	150 to 650 ppm 4 months to 15 yrs.
1972	22	Chang	0 among 119 workers	"	-	about 20 ppm; as low as 10.1 ppm
1973	31	Erdogen	13	shoes	-	"
1973	17	Biscaldi	1	furniture finishing	-	8 yrs.
1973	48	Kahn*	0	"	-	1.6-15.6 ppm
1973	51	Lange	10	painters	-	1 to 15 yrs
1973	66	Roth	19		-	
1973	73	Smolik	34	"	-	0.011 to 0.022 mg/liter 0.25 to 18 yrs.
1973	74	Sobczyk	80	plastics	-	0.5 to 10 yrs.
1974	57	McMichael*	0	rubber	-	general<25 ppm

maximum 125ppm

TABLE 1. continued

year	reference	first author	number of cases	type of manufacture	non-occupational exposure	exposure assessment
1975	72	Shima	0	varied small factories	-	25,013 person yrs. 1970-74
1976	10	Aksoy	8	shoes	-	210 to 650 ppm 1 to 15 years
1978	46	Iwata	1	*	*	*
1978	76	Townsend	0 among 282 workers	chemical	-	<2 ppm twa to 25=ppm twa. mean cancer exposure range of 256-1605 grams
1978	32	Fishbeck	0 among 10 workers{subset of Townsend, 1978 immediately above}			exposure of>24 ppm. 2 yrs. 6 months to 22 yrs, 11 months
1979	59	Pagnotto	0 among 37 workers	rubber coating	-	1 to 24 yrs, 5 to 140 ppm
1980	65	Roodman	1	-	marathon runner using rubber cement to attach adhesieve to foot blisters.	2-3 hours daily for 12 months
1980	44	Hisanga	2	overglaze decoration	-	*

* notes to table 1;

Greenberg (1939): Clinically significant cytopenias were found among 23 workers, and statistically significant declines in hemoglobin hematocrit and wbc were also reported.

Gadrat (1959): All reports were of leucopenia only.

Roth (1970): Altered lymphocytes and monocytes were found among 23% of 155 workers studied.

Kahn (1773): Increased -aminolevulinic acid was found.
All cell counts were normal.

McMichael (1974): An increased incidence of lymphoma and leukemia was suggested, see also Pagnotto et al (1961).

An asterisk (*) has been placed in the table when documents or translations were unavailable. These citations were included, nonetheless, for purposes of competeness.

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Table II

Leukemia

A. Acute Myelogenous Leukemia

year	reference	first author	number of cases	type of manufacture	non-occupational exposure	exposure assessment
1932	90	Emile-Weil	1	*	-	*
1937	116	Sabrazes	1	mirrors	-	qualitative
1937	122	Tzanck	1	rubber	-	13 years
1939	91	Erf	1	rubber	-	1 year
1941	123	VanRavenstyn	1	rubber	-	3 years
1942	106	Loeper	1	raincoats	-	5 years (ended 5 yrs. before onset)
1945	117	Saita	1	printing	-	5 years
1948	58	Oldfelt	1	*	-	*
1959	98	Guasch	1	*	-	*
1959	100	Justin-Besancon	1	dyes	-	13 years (ended 27 Yrs. before onset)
1962	24	Curletto	1	*	-	*
1962	53	Ludwig	2	chemical	-	14 & 19 years
1962	118	Saita	4	varied	-	*
1962	26	Degowin	1	painter	-	13 years (15 yrs. after recover from aplastic anemia
1963	120	Tareeff	5	printing and unspecified shoes,leather	-	13,17,22 years
1964	111	Pollini	1	*	-	*
1964	125	Vigliani	6	varied	-	3 to 19 years
1967	126	Zini	1	*	-	14 years
1971	112	Pugni	1	shoemaker	-	40 years
1971	119	Sellyei	1	*	-	18 month, 200-1640mg/m3 210ppm
1972	80	Aksoy	4	shoemakers	-	6,8,10,14 years
1972	115	Robustelli DellaCuna	1	*	-	6 years
1976	10	Aksoy	14	shoemakers		2-15 years, mean 10 years 4 months
1977	99	Infante				
1981	114	Rinsky				

Table II (continued)

B. Erythroleukemia

year	reference	first author	number of cases	type of manufacture	non-occupational exposure	exposure assessment
1950	93	Galavotti	1	shoemaker	-	19 years
1952	107	Nissen	1	*	*	*
1957	13	Appuhn	1	*	*	*
1958	87	DiGuglielmo	1	Rotograuure	-	4 years
1958	88	DiGuglielmo	1	*	*	*
1959	104	Kuhlmann	1	*	*	*
1963	119	Tareeff	2	varied	*	20-22 years
1967	103	Kohli	1	Shoemaker	-	19 years
1969	92	Forni	1		-	7 years
1976	10	Aksoy	6	Exposure details in Acute Myelogenous Leukemia		

C. Acute Monocytic Leukemia

1972	90	Aksoy	1	Shoemaker	-	lo years
1976	9	Aksoy	2	Exposure details in Acute Myelogenous Leukemia		

D. Chronic Myelogenous Leukemia

1949	124	VanSchoonoven	1	*	*	*
1951	84	Bousser	5	*	-	*
1961	101	Kahler	1	*	*	7 years
1963	120	Tareeff	5	varied	-	4 to 27 years
1967	96	Goguel	13	*	-	
1973	105	Liaudet	1	Petroleum Chemist	-	17 years
1976	10	Aksoy	1	Exposure details in Acute Myelogenous Leukemia		

E. Acute Lymphoblastic Leukemia

1928	86	Delore	1	*	-	5 years
1966	43	Hernburg	1	*	*	*
1967	97	Goguel	2	varied	*	*
1976	10	Aksoy	4	Esposure details in Acute Myelogeneous Leukemia		

F. Chronic Lymphocytic Leukemia

1947	89	Drouet	1	fabrique de chausseurs(Fr)	-	13 years
1954	110	Poinso	1	*	*	*
1963	119	Tareeff	3	varied	-	10 to 22 years
1965	102	Kiec	1	Paints & Laequers	-	40 years
1965	79	Bogetti	1	falegname(Je)	-	14 years
1966	95	Girard	1	*	-	12 years
1967	97	Goguel	8	varied	-	*
1972	80	Aksoy	0	Exposure details in Acute Myelogenous Leukemia		

Table II (continued)

G. Lymphoma/Soft Tissue Cancer

year	reference	first author	number of cases	type of manufacture	non-occupational exposure	exposure assessment
1939	55	Mallory	1(possible Hodgkins - Occupational exposure			
1948	83	Bousser	1(Lymphosarcoma) - Occupational exposure			
1963	119	Tareeff	2(Atypical Reticulosis and Plasmagtosis) - Occupational exposure			8 & 22 years
1965	108	Paterni	1(Reticulum Cell Sarcoma) - Printing Industry			
1969	85	Casirol	1(Lymphoma)			
1970	120	Torres	2(Multiple Myeloma) - Occupational exposure for 6 & 11 years			
1974	81	Aksoy	6(Hodgkin's) - Exposure details in Acute Myelogenous Leukemia)			

H. Myelofibrosis and Myeloid Metaplasia

1938	94	Gall	1		-	4 years
1941	112	Rawson	3	Shoe, Painting Machine Cleaning	-	5,16 & "many" years
1960	56	McLean	1	Occupational	-	1 year
1975	82	Aksoy	1	*	-	*

I. Thromboeythemia

1972	80	Aksoy	1	Shoemaker	-	10 years

Additional Occupational Investigations

Rubber Workers: Pagnotto et al. (1961, 1969); McMichael et al. (1974, 1975); Andjelkovic et al. (1976, 1978); Manson and Nakano (1976); Infante et al.(1977); Rinsky et al. (1981)

Printing Industry: Hoyd et al. (1977); Green et al. (1980).

Petrochemical Industry: Thorpe (1974); Theniant and Goulet (1979); Hanis et al. (1979); Thomas et al. (1980); Tushtar and Alderson (1980, 1981).

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TABLE III. OTHER POTENTIAL HAZARDS

A. Adverse Reproductive Effects (Barlow and Sullivan, 1982).

Year	First Author	Effects	Study Design
1965	Michon	Prolonged/Heavy Menses	500 women, 20-40 years of age, in a Polish factory producing leather and rubber shoes with Benzene ≤ 31 ppm, Toluene ≤ 67 ppm, Xylene ≤ 5[illegible] ppm were compared with 100 non-exposed controls.
1971	Mukhametova	Menstrual Disorders (Hyperpolymenorrhea 10.6% versus 3.2% in controls; acyclical disturbances 6.1% versus 1.9%). Spontaneous abortion (17.2% 4.9%). Late toxicoses (16.8% versus 8.4%); Premature birth (11.2% versus 4.2%); Threatened abortion (4.0% versus 1.5%). Incorrect implantation and detachment of the placenta (8.8% versus 4.2%); Fetal asphyxia (6.8% versus 2.6%); Higher perinatal mortality (6.3% versus 1.8%).	360 women, 20-40 years of age, working as gluing operatives in a mechanical-rubber product factory were studied. Petroleum and chlorinated hydrocarbons (including dichlorethane and methylene chloride) were included in the exposures. 616 women of comparable age but without exposure were used as controls. Induced abortion was the most common outcome of pregnancy in both groups. Only 65 births occurred among exposed and 79 in controls.
1959	Ragucci	7 spontaneous abortions, one stillbirth, 3 cases of uterine inertia, 4 normal births	Case Series of Benzene Poisoning in in Pregnancy.
1957	Riera-Barta	Maternal death due to hemorrhage	Case of Benzene Related Aplastic Anemia
1972	Messerschmitt	2 abortions at 5 months, one delivery at 7 months, 4 maternal deaths, 3 child deaths.	5 case reports of pregnant women with benzene associated aplastic anemia.

B. Cardio/Cerebro vascular (only abstracts were available in translation).

Year	First Author	Effects	Study Design
1973	Monaenkova	Hypotonia of cerebral vasculature.	Case series of 117 patients with occupational poisoning including 28 with benzene poisoning.

TABLE III. OTHER POTENTIAL HAZARDS (continued)

B. Cardio/Cerebro vascular (continued)

Year	First Author	Effects	Study Design
1974	Reznik	Ischemic heart disease; arterial hypertension Among cases, 26.6% had ischemic heart disease, and 52% had either arterial hypertension or arterial pressure within the limits of a "transition zone" (undefined). Frequencies exceeded those among controls by three and two times respectively.	150 patients with a 15 - 26 year history of chronic poisoning with benzene derivatives were compared with controls.
1979	Karmaz	Hypercholesterolemia, Hyperphosphatipidemia	250 workers in coke-benzene production were compared with 120 workers not having contact with 120 workers having contact with aromatic hydrocarbons.

C. Neurologic/Psychologic

Abnormal EEG

1969	Schneider	82% of benzene exposed workers had abnormal EEG findings.	Case series of 71 workers age 30 $\pm$ 1 years with 4.6 $\pm$ 0.4 years of exposure (Abstract only).
1973	Sobczyk	40 % of workers examined had abnormal EEGs.	Case series of 100 women employed at gluing of plastic elements at a Polish factory. All 100 had experienced symptoms and signs of benzene poisoning 3 to 4 years prior to EEG. (Abstract only).
1985	Kellerova	13 (32.5%) of benzene exposed had a normal EEG versus 40 (83.3%) of the non-exposed. 18 (45%) versus 6 (12.5%) had a threshold response and 9 (22.5%) versus 2 (4.2%) were abnormal. Abnormalities in the benzene exposed were episodic, diffuse or a combination of the two.	Case-control study of 40 benzene exposed workers (28 with benzene concentrations of 145-500 mg/m^3 up to 1000 mg/m^3 and 12 with benzene concentrations, "Only exceptionally" in excess of HPCP. Exposed included 37 men and 3 women. Controls were 48 healthy persons (42 men and 6 women). Average age of the 28 highly exposed was 32.4 years and exposure durations was 0.5-4 years. Average age for the 12 (continued)

TABLE III. OTHER POTENTIAL HAZARDS (continued)

C. Neurologic/Psychologic (continued)

Abnormal EEG (continued)

Year	First Author	Effects	Study Design
1985	Kellerova (continued)		with generally acceptable exposure was 41.5 years and exposure duration was 2-20 years. Comparisons were 20-53 years old. Additional comparison was made with a toluene-xylene exposed group and a vinyl chloride exposed group. Othe than age-sex differences, other potentially confounding factors were not discussed. Reference is made to eight previous EEG studies involving isolated cases.
	Physical Assessment		
1971	Drogichina	95% of patients with chronic benzene poisoning had abnormalities including: asthenoneurotic, astheno-vegetative, vegetative polyneuritis, asthenic and astheno-organic polyneurites.	Case series of 250 patients with chronic benzene poisoning (Abstract only).
1984	Herregods	Transverse myelitis	Case report of benzene poisoning
	Psychologic		
1973	Korolenko	Various substances were studied with several abnormalities noted. Abnormalities specifically associated with benzene were not defined.	Case series of 142 persons suffering from chronic lead, ethylated petrol, mercury and benzine poisonings (Abstract only).
D. Immunologic			
1980	Moszczynski	Increased activities of acid phosphatase, beta-glucuronidase, NBT reduction and diminished glycogen reserves in peripheral blood neutriphils. These changes were accompanied by diminished peroxidase and alkaline phosphatase activities. Stimulated NBT production was negatively correlated with duration of exposure.	Cross sectional survey of 106 workers in contact with organic solvents containing benzene and its homologues for periods up to 122 months (Abstract only).

TABLE III. OTHER POTENTIAL HAZARDS (continued)

Immunologic (continued)

Year	First Author	Effects	Study Design
1982	Moszczynski	In workers with more than 55 months exposure, decreased T and non-T, non-B lymphocyte count is noted. Monocytes are increased.	Same population as previous entry. (Abstract only).
1983	Moszczynski	Progressing reduction of numbers of lymphocytes having AP-positive intact lysosomes.	108 workers with 31-122 months of exposure to benzene, toluene and xylene (0-370, 0-580 and 0-560 mg/eum respectively. (Abstract only).
1984	Moszczynski	N-acetyl-beta-D-glucosaminidase (NAG) deficiency in peripherals lymphocytes.	Same population as above.
1984	Moszczynski	Decreased T lymphocyte count without alterations in their functions.	72 workers with occupational contact with benzene, toluene or xylene. (Abstract only).
1981	Chirco	Increased endolymphocytic RNA. Increased capacity of immunoglobulin formation, particularly IgM. All are considered as early signs of enhanced immune reactivity.	270 workers with chronic benzene
E. Miscellaneous			
1970	Klavis	Goodpasture Syndrome [glomerulonephritis, intra-alveolar pulmonary hemorrhage, antiglomerular basement membrane antibody]	Case Report (Abstract only) Heavy benzene exposure.
1976	Dickson	High pressure injection injury of the hand. Widespread vessel thrombosis, absence of fat from fat loculi and coagulative necrosis of skin and subcutaneous tissue.	A case which led to digital amputation is described.
1958	DiGuglielmo	Segmented spontaneous infarction of the Greater Omentum.	Case reports (Abstract only).

TABLE III. OTHER POTENTIAL HAZARDS (continued)

E. Miscellaneous (continued)

Year	First Author	Effects	Study Design
1971	Csata	Nephrotoxic Anuria	Case report of severe poisoning due to a combination of benzene, chloroform and acetone.
1977	Guingatullina	Reduced intra-ocular pressure and transitory hypersecretory [intraocular] hypertension without marked changes in the blood supply of the ciliary body.	Cases and controls were studied. No further description is provided. (Abstract only).

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