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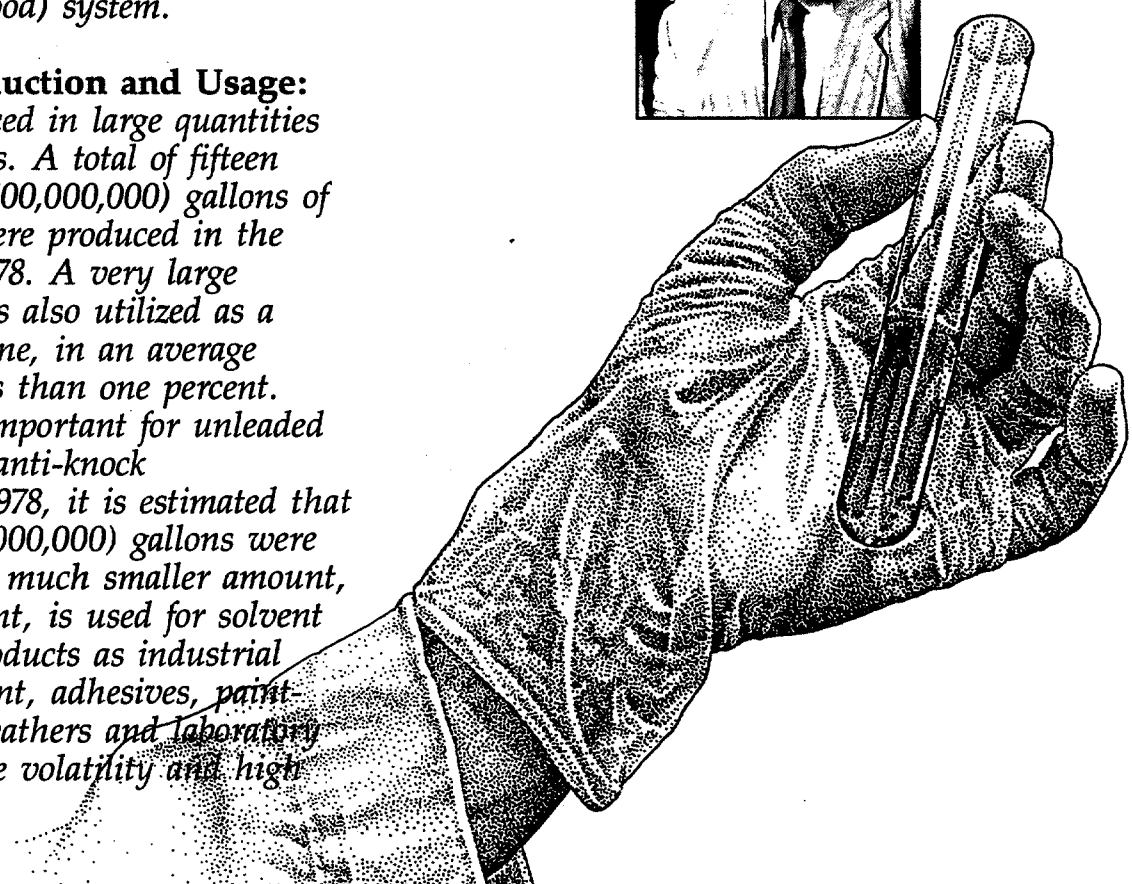
An etiologic association between benzene and leukemia was suggested approximately 50 years ago. Over the years, these observations were corroborated by epidemiologic studies and recently by carcinogenic bioassays. Benzene is now considered, by national and international scientific and health organizations, to be a human carcinogen. The purpose of this review is to summarize the available information on benzene and its effects on the hematologic (blood) system.

Industrial Production and Usage:

Benzene is produced in large quantities in the United States. A total of fifteen hundred million (1500,000,000) gallons of industrial grades were produced in the United States in 1978. A very large portion of benzene is also utilized as a component of gasoline, in an average concentration of less than one percent. Benzene is highly important for unleaded fuels because of its anti-knock characteristics. In 1978, it is estimated that 1650 million (1650,000,000) gallons were used in gasoline. A much smaller amount, less than two percent, is used for solvent purpose in such products as industrial paints, rubber cement, adhesives, paint-remover, artificial leathers and laboratory solvents. Due to the volatility and high



BENZENE and DISEASES of the BLOOD

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solubility of benzene it has the potential to migrate in the environment and contaminate water directly, and enter surfaces where water can penetrate. Microbial degradation of benzene has been described indicating that biodegradation probably occurs naturally, but this process is slow.

Populations highly exposed to benzene are as follows: 1) workers engaged in its production, 2) workers engaged in chemical industries utilizing benzene, 3) workers in industries producing materials containing benzene, 4) workers utilizing or handling compounds containing benzene, 5) people living near factories producing or utilizing benzene. (Table 1 describes the industrial exposures to benzene).

The level of benzene allowed in the workplace varies from country to country. Until 1978, in the USA, the OSHA standard for benzene was 10 ppm with an acceptable ceiling concentration of 25 ppm. In 1978, OSHA stated that 1 ppm with a 5 ppm ceiling limit for 15 minutes during the eight-hour day is the level which most adequately assures, to the extent feasible, the protection of workers exposed to benzene. That rule was annulled by the U.S. Supreme Court.

The level allowances of benzene in other countries are as follows: 10 ppm in Italy, Belgium, Holland, Poland, Sweden and Switzerland; 25 ppm in Austria and Japan; 15 ppm in Czechoslovakia, Yugoslavia and East Germany.

Route of Human Exposure:

Human exposure to benzene is by the following: 1) Ingestion of water and other fluids. 2) Ingestion of food. 3) Inhalation. 4) Dermal absorption.

Although benzene is relatively soluble in water, the magnitude of human exposure through water is probably negligible. Only trace levels of benzene have been detected in few fresh water samples in recent studies by the EPA.

The respiratory route is the primary source of human exposure to benzene. Much of this exposure to the general population is by way of gasoline vapors and automobile emissions. American gasoline contains an aveage of less than 1% benzene. Ambient air concentrations of benzene in the vicinity of gas stations ranged from 0.2 ppm to 0.9 ppm. In industrialized areas and heavily congested areas, levels of 15 ppm all the way to 57 ppm were described.

The following have been described as the most common and important sources of ambient benzene: chemical manufacturing facilities, coke ovens, petroleum refineries, solvent operations, gasoline storage and distribution centers, self-service gasoline stations and automobile emissions and evaporation from gasoline service stations. Half of the US population is exposed to atmospheric benzene concentration in the range of 0.1 to 4 ppm with nearly a quarter of the population exposed to concentrations within the range of 1.1 to ppm, many from automobile emissions.

Smoking may be a very significant benzene exposure source for a portion of the population. Studies have described that an individual who smokes one pack of cigarettes per day may be exposed to 28 ppm of benzene per day. Benzene is poorly absorbed through the skin and skin contact is infrequent. Therefore, the skin route is probably an insignificant source of exposure for the general population.

Effects of Benzene on the Hematological System:

To date, a long list of hematologic disease has been linked directly to benzene exposure (Table III).

Benzene has been known as a hematologic poison since the nineteenth century when aplastic anemia in workers fabricating bicycle tires was described. Many other hematological diseases have been reported since to be the result of benzene exposure. Lack of knowledge regarding the mechanisms and toxicity leaves the issue of dose open. It is probable that some hematological disorders related to benzene may not be dose-dependent but rather represent an idiosyncratic (allergic) reaction of the blood system or direct toxicity of breakdown products of benzene in the human body. On the other hand, recent studies indicate a direct correlation between dose exposure over the years and benzene related diseases.

A. Aplastic Anemia/Pancytopenia:

Aplastic anemia is a realtively rare, often fatal disorder in man. Its diagnosis is usually made on the basis of a significant reduction in the formed elements of the blood, including decreased white blood cells, anemia, and thrombocytopenia. A decrease in all three of these blood cells counts is defined as pancytopenia. A marked decrease in the number of cells in the bone marrow is called aplastic anemia. It is accepted that these two are not two separate diseases but rather a spectrum of bone marrow failure secondary to benzene toxicity. Indeed, a complete evaluation of a work force in a benzene-using plant revealed many affected individuals with effects ranging from a mild cytopenia to aplastic anemia of sufficient severity to warrant hospitalization; levels of exposure were 10-400 ppm of benzene.

The time of development of aplastic anemia or thrombocytopenia in relation to the exposure dose is of great interest. The following studies have been described: (1) A followup sudy of 125 workers in a shoe factory who were exposed to levels of 400 ppm of benzene, 9 years later noted some persistent cytopenias. One individual had developed acute leukemia and died. (2) Four individuals were reported to have persistent decrease in blood counts and one patient had died of aplastic anemia 9 years after cessation of exposure. (3) An outbreak of hematological toxicity in leather workers in 1975 was directly temporaley related to the use of an adhesive containing benzene beginning in about 1960. (4) Thirty-two cases of significant aplastic anemia in people exposed to benzene for 4 months to 15 years were reported in the literature. Exposure levels ranging from 150 to 650 ppm were reported. (5) In another study, 51 of 217 apparently healthy workers were found to have some hematological abnormalities including 6 cases of pancytopenia. These workers are described as having been exposed to 30 to 210 ppm benzene for 3 months to 17 years.

This data indicates that aplastic anemia and thrombocytopenia in relation to benzene exposure may develop as soon as several months or up to 17 years.

The clear temporal relationship between the onset and cessation of hematological abnormalities and the use of benzene provides further evidence allowing the conclusion that causal relationship between benzene exposure and pancytopenia and anemia is sound.

B. Acute Myeloblastic Leukemia:

Acute myeloblastic leukemia is a cancer of the blood system in which there is an abnormal production of the hematologic stem cells, for granulocytic leukocytes, red blood cells and platelets. This disease is mostly observed in adults and has an increasing incidence with age, peaking in the 6th or 7th decade. There are a number of

variants of acute myelogenous leukemia which can be considered to be part of the same disease. These include acute myelomonocytic leukemia, promyelocytic leukemia, and erythroleukemia.

The medical literature has a wealth of cases of acute myeloblastic leukemia in which benzene exposure has been reported as the causative agent. The relatively common description of aplastic anemia associated with benzene exposure followed through a pre-leukemic phase into acute leukemia further in support of the notion that bone marrow toxicity of benzene is a wide spectrum of diseases, and pending the severity has presented as anemia, thrombocytopenia or leukemia.

As for aplastic anemia, the dose of exposure and time of development of leukemia varies from several months up to 27 years after cessation of exposure.

Taken together, these reports provide strong evidence of a casual relationship between benzene exposure and development of acute myeloblastic leukemia.

A recent study in the New England Journal of Medicine (for reference: **New England Journal of Medicine,** 1987, April 23, page 1044), quantitatively assessed the relation between benzene exposure and leukemia and examined the mortality rate of a cohort with occupational exposure to benzene. Their findings are summarized in the following statements: (1) There is a strong positive exposure response relation betweeen benzene and leukemia. (2) On the basis of their study, they conclude that exposure levels of less than 1 ppm annually, cumulative over a 40-year working lifetime, may have been the exposure causation for leukemia. (3) In the population studied, there was a statistically significant excess of death from multiple myeloma (multiple myeloma is another hematological abnormality, whereby not related to the leukemia lymphoma group, it is still a chronic and many times hematological disease of the bone marrow). Of interest in this study is a description of a patient who died from leukemia 34 years after his exposure to benzene which was 19.56 ppm over the years. Multiple myeloma, the cause of death in four members in this study, was described previously in relation to benzene, although in small numbers. Furthermore, it is of interest that these patients have a very long latency period from the time of exposure of over 20 years, and the lowest cumulative exposure of 40 ppm years.

C. Lymphoma and Lymphatic System:

Recently, studies aimed at evaluating the effects of benzene and leukemia have also shown an increase in the relative risk of lymphatic system malignancies in benzene workers. A recent study by NIOSH, described increased mortality from lymphoma and lymphocytic leukemia. A similar increased risk for lymphatic cancer was reported by other groups. Rubber chemical workers who were exposed to benzene had 4 to 5 fold higher risk of lymphoid malignancy than those unexposed. The mechanism of benzene toxicity and lymphatic system cancers is not clear. While with leukemia and aplastic anemia, the mechanism is direct toxicity of the bone marrow system, with the lymphatic system, the mechanism is unclear.

TABLE I
POTENTIAL INDUSTRIAL EXPOSURES TO BENZENE

1. DETERGENT PRODUCERS.
2. PESTICIDE PRODUCERS.
3. GASOLINE PRODUCERS.

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4. SOLVENT PRODUCERS.
5. PAINT AND VARNISH PRODUCERS.
6. ADHESIVE PRODUCERS.
7. RUBBER INDUSTRY PROCESSORS.
8. PETROLEUM INDUSTRY PROCESSORS.
9. CHEMICAL WORKERS.

TABLE II
BENZENE EXPOSURE AND HEMATOLOGIC DISORDERS

A. CAUSATION PROVEN
   1. APLASTIC ANEMIA, PANCYTOPENIA.
   2. ACUTE MYELOGENOUS LEUKEMIA.
   3. ERYTHROLEUKEMIA.
   4. MYELOMONOCYTIC LEUKEMIA.
   5. ACUTE PROMYELOCYTIC LEUKEMIA.

B. CAUSATION PROBABLE
   1. CHRONIC MYELOGENOUS LEUKEMIA.
   2. CHRONIC LYMPHOCYTIC LEUKEMIA.
   3. HODGKIN'S DISEASE.
   4. PAROXYSMAL NOCTURNAL HEMOGLOBINURIA.

C. CAUSATION HIGHLY SUSPECTED
   1. MULTIPLE MYELOMA.
   2. ACUTE LYMPHOBLASTIC LEUKEMIA.
   3. LYMPHOMA.
   4. THROMBOCYTHEMIA.

Safety and Policy:

To reduce the risk of leukemia in industrial workers exposed to benzene, the United States Occupational Safety and Health Administration (OSHA) in 1978 reduced the permissible workplace exposure of benzene from previous 10 ppm to 1 ppm. However, in 1980, the U.S. Supreme Court invalidated the OSHA benzene standard of 1 ppm. The court stated that "OSHA had failed to provide substantial evidence of the need for regulation, and that it had not deomonstrated a significant risk of material health impairment at the previous level of 10 ppm." (**New England Journal of Medicine,** 1987, April, Page 1044). Since then, three studies have been published, in each of which the amount of benzene exposure has been found to correlate strongly with the risk of death from leukemia. The most recent study published in the New England Journal of Medicine on Benzene and Leukemia further demonstrates that a cumulative benzene exposure of 44 ppm years is equivalent to a mean annual exposure of 10 ppm over a 40-year working lifetime. Ten ppm is the currently enforceable standard in the United States for occupational exposure to benzene. They concluded that protection from benzene-induced leukemia would increase exponentially with any reduction in the permissible exposure limit enforceable to date. Obviously, the crucial question of who will develop a hematological disease as a result of exposure at the workplace to benzene is impossible to answer scientifically. Although a dose relation has been demonstrated, the fact that some cases have been described where exposure to benzene was not at excessive levels suggests that even ideally strict protective efforts may not completely prevent industrially-related benzene exposure and hematological cancers. It is, however, encouraging, based on the recent study in the **New England Journal of Medicine,** that strict enforcement of the permissible levels will significantly and exponentially reduce the risk of hematological cancers from

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exposure to benzene.

How to Make or Rule Out a Diagnosis of Benzene-Related Hematological Disease:

The examining phyisican who is faced with the question of causation in a patient with hematological malignancy and benzene exposure must utilize epidemiologic and scientific data in his evaluation. It is imperative that material safety data sheets as well as job analysis description and investigative report, specifying the exact frequency and amount of exposure of benzene levels in the air, be studied. The examining physician must request information in relation to other exposures such as solvents and pesticides. The time elapsed from the last exposure to benzene must also be taken into account. In some instances, it is probable that both the exposure to benzene on an industrial basis and exposure to other toxic chemicals on a nonindustrial basis may be additive. In other instances, it is probably the exposure to nonindustrial toxicants may be responsible for the hematological cancer rather than the benzene, pending information available on exposure levels and frequency. As an example, I will discuss a case of leukemia in a 68-year-old petroleum engineer. His leukemia was diagnosed 10 years after his last exposure to benzene (he was exposed over a period of 16 years at a total level of 1600 ppm). During the 10 years prior to diagnosis of leukemia he worked as a desk supervisor with no exposure to benzene or any other chemicals. An investigative report, job analysis and material safety data sheets clearly showed no other exposures to chemicals (such as nonindustiral) and very clearly indicated a daily exposure to benzene with its inhalation over a period of 16 years! Based on the levels of exposure, safety data sheets and absent any other chemical exposure, the latency period of 10 years was compatible with the diagnosis of benzene induced leukemia.

(Table III summarizes the information required for evaluation of industrial causation in a leukemia or lymphoma case in relation to benzene).

TABLE III
INFORMATION REQUIRED IN THE ANALYSIS OF BENZENE EXPOSURE AND HEMATOLOGICAL MALIGNANCIES

1. JOB ANALYSIS DESCRIPTION WITH DETAILED EXPOSURE HISTORY.
2. AIR LEVEL MEASUREMENT.
3. INVESTIGATIVE REPORT.
4. NONINDUSTRIAL EXPOSURE TO SOLVENTS, PESTICIDES & HERBICIDES.
5. INDUSTRIAL EXPOSURE TO SOLVENTS, PESTICIDES & HERBICIDES.
6. LATENCY PERIOD: TIME FROM LAST EXPOSURE.

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4. *P. Decoufle, et al. "Mortality Among Chemical Workers Exposed to Benzene and Other Agents", Environmental Research, 9183; 30-16-25.*

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CWCI RELEASES DWC 500 INSTRUCTIONAL MATERIALS

The California Workers' Compensation Institute has produced a series of audiotapes, a workbook and a user's manual to introduce claim technicians to the new DWC 500 letters which insurers and self-insured employers will be required to use as of January 1.

The materials cover the revised employee notification regulations adopted by the DIA administrative director last June. The major change involved 14 variations of the basic DIA 500 form letter dealing with payment of temporary disability, permanent disability, death benefits, notice of delay or denial of benefits, and disability rate changes.

The audiotapes, recorded at CWCI's workshop, "Interpreting and Applying the New DIA 500 Regulations," are available for $25 a set. The workbook syllabus serves as a guide through the taped material, and is available for $5 a copy. The revised Benefit Instruction Manual, including guidelines for completing all 14 letters, also is $5 a copy.

Orders may be mailed to CWCI, 120 Montgomery Street, Suite 1300, San Francisco, 94104. The Cost of the materials, plus California sales tax and delivery charges, will be billed upon shipment. Allow four to six weeks for delivery.