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COMMENTARY

Benzene Health Effects: Unanswered Questions Still Not Addressed

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INTRODUCTION

In 1985 the ***American Journal of Industrial Medicine*** reviewed then-available information on the health effects of benzene (Volume 7). It was clear that our knowledge of benzene's effects in a number of significant areas of investigations was still incomplete. We did not know at what level of exposure benzene became overtly hazardous in terms of human disease. Data were lacking concerning a potential "practical threshold dose" **below** which overt adverse effects do not occur in exposed individuals. This critical information could be obtained from a series of long-term, chronic, low-level benzene exposure studies in experimental animals, using a wide dose distribution between 0.1 and 50 ppm which could, in conjunction with biochemical mechanistic studies, be used to help evaluate a "no effects'' level. Such a "practical threshold level" could be used as a basis for consideration of regulation. At the time, I recommended to the benzene-manufacturing industry that research be undertaken to answer questions relative to bone marrow damage, i.e., is such a phenomenon a necessary precondition for the development of human leukemias, a malignancy known to be caused by benzene. If this were the case, could it then serve as a means for early detection and prevention of harmful effects, namely, leukemias and other cancers due to benzene exposure? Eight years later, the issues are still largely unaddressed.

Benzene, a significant component of gasoline, has been shown to be a carcinogen in both animals and humans (Mehlman. 1990; EPA, 1984, 1986; Tironi et al.. 1986; Westberg and Lamb, 1985; Machle, 1941; Poklis and Burkett, 1977). At one time, benzene was widely used as a solvent, present in inks, rubber, lacquers. paint remover, and many other products. Total benzene usage today is approximately 11

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billion gallons per year [ACGIH, 1990] and it has been estimated that 238,000 people are occupationally exposed to benzene in petrochemical plants, petroleum refineries, and other operations. Benzene is currently classified by EPA and IARC as a human carcinogen.

EXPERIMENTAL CARCINOGENESIS

In numerous studies, Maltoni et al. [Maltoni, 1982a,b, 1983; Maltoni and Scarnato, 1977, 1979; Maltoni et al., 1982a,b,c,d, 1983a,b, 1985. 1987] demonstrated that benzene caused tumors in rats and mice including cancer of the zymbal gland, cancer of the oral cavity, lymphoma, cancer of the lung, cancer of the skin, cancer of the nasal cavity, cancer of the forestomach, cancer of the harderian gland, cancers of mammary gland, ovary, and uterus, hemolymphoreticular neoplasia, and all types of leukemias. Huff et al. [1989] expanded these studies, using a broader dose range, and reported numerous cancers, occurring at a lower dosage, in various organs and tissues.

Infante and White [1985] calculated the excess of death from leukemia per 1,000 workers exposed to benzene for an occupational lifetime. The relative risk of death from leukemia was calculated from 3.75 to **25,** depending on the level and duration of exposure.

EARLIER KNOWLEDGE

Earlier data on benzene-caused carcinogenicity in humans were based on a number of clinical cases of leukemias in humans occupationally exposed to benzene. The 1928 report by Delore and Borgomano and the 1932 report by Lignac were followed by a variety of reports from Italy [Vigliani, 1976; Vigliani and Saita. 1964], France [Goguel et al.. 1967; Girard et al., 1968, 1970, 1971a,b; Girard and Revol. 1970], and Turkey [Aksoy et al., 1972. 1974]. Goldstein in 1977, in a comprehensive review of the literature on benzene, compiled case reports on benzene-exposed individuals with hemolymphoreticular cancers. The types of leukemias found in these individuals were acute myelogenous leukemia. erythroleukemia, acute myelomonocytic leukemia, chronic myelogenous leukemia. myelofibrosis, and myeloid metaplasia, thrombocytopenia, acute lymphoblastic leukemia, chronic lymphocytic leukemia, lymphomas, and other related cancers.

While there is larger prevalence of acute myelogenous leukemias, it has been found that all forms of leukemia can be caused by benzene. In 1971. lshimaru et al. reported leukemia in adult survivors of Hiroshima and Nagasaki. This report noted that the risk of leukemia was two and a half times greater among individuals who. in addition to radiation, had also been occupationally exposed to benzene.

HUMAN NEOPLASMS

The types of leukemias caused from exposure to benzene include acute myelogenous leukemia, acute lymphocytic leukemia, acute erythroleukemia, leukemia. acute myelomonocytic leukemia, acute promyelocytic leukemia, acute undifferentiated leukemia, hairy cell leukemia, chronic myelogenous leukemia, chronic lympho-

cytic leukemia, Hodgkin's lymphoma, non-Hodgkin's lymphoma, and multiple myeloma.

In 1939 Hunter reported that benzene causes human cancers. Recently Yin et al. [1989] reported significant increases in human cancers from exposure to benzene. Benzene caused leukemia and cancers of the lung, liver, lymphosarcoma, stomach, esophagus nasopharynx, and intestine.

REGULATION

The threshold limit value-time weighted average (TLV-TWA) for benzene in 1946 was 100 ppm; in 1947, 50 pprn; 1948–1956, 35 ppm; 1957–1962, 25 ppm; 1977–1987, 10 ppm; and it is currently 1 ppm. In July of 1990, the American Conference of Governmental Industrial Hygienists (ACGIH) recommended that the TLV-TWA for benzene be reduced to 0.1 ppm.

The American Petroleum Institute (API) in September of 1948, issued a document entitled "API Toxicology Review: Benzene," prepared by P. Drinker and widely circulated to oil companies. This report states, "Inasmuch as the body develops no tolerance to benzene and there is a wide variation in individual susceptibility, it is generally considered that the only absolutely safe concentration for benzene is zero.''

The API document further stated that "a limit of 50 pprn or less is strongly recommended, particularly where exposures are recurrent. Skin contact should be avoided." This API document recommended level was 500-fold greater than that recently recommended by ACGIH. Thus, in spite of scientific evidence and general knowledge of the carcinogenicity of benzene, it is disconcerting that warning labels are not utilized to identify the carcinogenicity of benzene in products containing this chemical, especially gasoline. The current benzene content of gasoline is between 1.5% and 6%.

SUMMARY

Data which could have helped answer many of the scientific questions posed in 1983 concerning the carcinogenicity of benzene are not yet available. Since we do not know of any safe level above zero, the problems that have been plaguing the health protection process relative to benzene can perhaps be best resolved by setting current recommended maximum levels of exposure to 0.004 to 0.1 ppm, and, to the extent possible, avoiding any exposure at all to benzene and benzene-containing products.

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