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A Review on Bezene and Haematological System

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Summary

Benzene is a chemical substance that is widely used in industrial setting, ranging from solvent to gasoline additives. This shows that benzene is ubiquitous based on our daily activities. Although benzene is widely used in industrial setting, it has a toxic effect on the system of haematology, reproduction and neurology. The most probable mechanism of benzene-induced leukemia is through its phenolic metabolites acting in concert to produce DNA damage. This leads to mitotic recombination, chromosome translocations, and aneuploidy.These genotoxic events will, in turn, cause the activation of protooncogenes, loss of heterozygosity, and inactivation of tumor suppressor genes. In recent years, the relationship between benzene and smoking-induced hematopoietic malignancies has been solidified. Benzene has been known as a haematologic poison. Bezene has effect on all the haematopoietic cells and this happens by lodging in the bone bone marrow , leading to production of abnormal cells.

Keywords : Benzene; Hematology; Reproduction; Neurology; Leukemia

Abbreviations : IARC: International Agency for Research on Cancer's; MDS: Myelodysplastic Syndrome; NHL: Non-Hodgkin's Lymphoma; OSHA: Occupational Safety and Health Administration; EPA: Environmental Protection Agency; API: American Petroleum Institute; SCEs: Sister Chromatoid Exchanges; FISH: Fluorescence *In Situ* Hybridization; SP: Spectral Karyotyping; PCR: Polymerase Chain Reaction

Benzene

Benzene is reported as a chemical substance that is widely used in industrial setting, ranging from solvent to gasoline additives. Benzene is found in the air out of the emissions from cigarette smoke,motor vehicle exhaust, burning coal and oil, and gasoline service stations [1]. This shows that benzene is ubiquitous based on our daily activities.Although benzene is widely used in industrial setting, it has a toxic effect on the system of hematology, reproduction and neurology.Workers who are overexposed chronically can be inflicted to anemia, leucopenia, and thrombocytopenia. The peripheral blood morphology shows some immature leukocyte such as band, metamyelocyte, myelocyte, or myeloblast [2]. Also, benzene is a cancer-causing carcinogen in workers exposed to high levels of workplace air. It is shown that hundreds of leukemia cases caused by benzene exposure have been reported from some industries, such as shoes industry, paint industry, and charcoal industry [3]. The occurrence of leukemia caused by benzene needs a long time exposure.

Similarly, epidemiological study shows that the leukemia cases increase gradually among the workers who work in high levels of benzene exposure. Benzene is one of the best studied of the known leukemia. The most probable mechanism of benzene-induced leukemia is through its phenolic metabolites acting in concert to produce DNA damage. This leads to mitotic recombination, chromosome translocations, and aneuploidy. These genotoxic events will, in turn, cause the activation of protooncogenes, loss of heterozygosity, and inactivation of tumor suppressor genes. If this takes place in the bone marrow stem, a leukemic clone with selective growth advantage can arise. Epigenetic effects of benzene on the bone marrow stroma can then assist in the establishment of a leukemic clone. In the oil and natural gas mining, the employees were exposed to benzene for a long time. Therefore, the possibility to get carcinogenicity effect from the benzene exposure is high [3].

Route of human exposure

Human exposure to benzene of significance is by the following:

a. Inhalation

b. Dermal exposure

c. Ingestion of water and other foods contaminated with benzene.

Although benzene is relatively soluble in water, commonly the magnitude of human exposure via water is probably negligible. The respiratory route is commonly 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. In industrialized areas and heavily congested areas, levels of 15 parts per billion (ppb) up to 57ppb were described, while the average background levels have been reported to be 2.7 to 20ppb.

Benzene is absorbed through the skin, but skin contact is infrequent for the non-working general population. While the skin route is probably an insignificant source of exposure

for the general population, it has been shown as a significant route of exposure in the working population [3]. Smoking may be a significant benzene exposure source for a portion of the population. Studies have described levels of benzene exposure in active smokers at the range of 7.2 to 17.8ppb.

In recent years, the relationship between benzene and smoking-induced hematopoietic malignancies has been solidified. Korte et al. [4] combined epidemiological data on the health effects of smoking with risk assessment techniques for low-dose extrapolation and assessed the proportion of smoking-induced total leukemia and acute myeloid leukemia attributable to benzene and cigarette smoke. This study was based on linear potency models. According to this study, benzene is estimated to be responsible for approximately one-tenth to one-half of smoking-induced total leukemia mortality and up to three-fifths of smoking related acute myeloid leukemia mortality. Kasim et al. [4] has recently reported that active smoking was observed to be associated with a substantial increased risk of leukemia (odds ratio, OR = 1.5, 95% confidence interval, C.I. = 1.1 to 2.0). The International Agency for Research on Cancer's (IARC) 2004 monograph on cigarette smoking states that cigarette smoking causes leukemia, and that cigarettes contain sufficient quantity of the leukemogen benzene. This is an important development in terms of leukemogenesis and low-level exposure to benzene. One pack of cigarettes a day for 20 years is equivalent to 15ppb cumulative benzene exposure. This relatively new recognition further supports benzene leukemogenicity at levels lower than 1ppm and based on IARC , levels as low as 15ppb [5].

Benzene has been known as a haematologic poison since the nineteenth century when aplastic anemia in workers fabricating tires was described. Many other hematological diseases have since been reported to be the result of benzene exposure. Many of the hematological disorders related to benzene may not be dose-dependent as the mechanism of these diseases are yet not completely understood, although it is strongly believed that benzene carcinogenicity is mediated via immune suppression and DNA cell changes.

Myelodysplastic syndrome

Myelodysplastic Syndrome (MDS) is a bone marrow diseases and is considered to be in a preleukemic stage. Several case reports, case studies, and epidemiological studies demonstrate that MDS is caused by benzene exposure at benzene exposure levels less than 10ppm. It has been suggested that benzene-induced MDS is an early or predisposing event in the pathogenesis of benzene-induced hematologic diseases [6]. The list of studies describing MDS caused by benzene includes.

Aplastic anaemia/Pancytopenia

Aplastic anemia is a relatively 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 are part of a spectrum of bone marrow failure syndromes which can result from 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 10-400ppm of benzene.

Acute myeloblastic leukemia

Acute myeloblastic leukemia is a cancer of the blood system in which there is an abnormal production of hematologic stem cells, granulocytic leukocytes, red blood cells and platelets. This disease is mostly observed in adults and has an increasing incidence with age, peaking in the 6^{th} or 7^{th} 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 is replete with cases of acute myeloblastic leukemia in which benzene exposure has been shown 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 supports the concept that the bone marrow toxicity of benzene encompasses a wide spectrum of diseases presenting as anemia, thrombocytopenia, leukemia, or the other hematological diseases.

A published study in the New England Journal of Medicine, by Rinsky et al. [7] quantitatively assessed the relation between benzene exposure and leukemia and examined the mortality rate of cohort with occupational exposure to benzene. Their findings are summarized in the following statements:

1. There is a strong positive exposure response relation between benzene and leukemia.

2. On the basis of their study, they conclude that exposure levels of less than 1ppm annually, cumulative over a 40-year working lifetime increases the risk of leukemia by a factor of 1.7.

3. In the population studied, there was a statistically significant excess of death from multiple myeloma (multiple myeloma is another hematological cancer, of plasma cells). Of interest in this study is a description of a patient who died from leukemia 34 years after his exposure to benzene levels of 19.56ppm 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 40ppm years. This paper also demonstrates a latency as short as 1 year.

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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 has been reported by other investigators. Rubber chemical workers who were exposed to benzene had 4 to 5 fold higher risk of lymphoid malignancy than those unexposed [8].

Non-Hodgkin's lymphoma

Several lines of evidence demonstrate that benzene causes non-Hodgkin's lymphoma (NHL). Italian investigators presented a paper at the April 2005 American Association of Cancer Research. For benzene exposures of 15 years duration, researchers showed a significant excess risk for NHL and demonstrated a dose-response relationship when considering NHL subtypes. In 2004, Scandinavian researchers reported the results of a case-control study for NHL and occupational exposures. Risk of NHL was significantly increased for exposure to gasoline, oil products, and solvents [9].

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 work place exposure of benzene from previous 10ppm to 1ppm. However, in 1980, the US Supreme court invalidated the OSHA benzene standard of 1ppm. The court states that AOSHA had failed to provide substantial evidence of the need for regulation, and that it had not demonstrated a significant risk of material health impairment at the previous level of 10ppm. 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 study published in the New England Journal of Medicine on benzene and leukemia further demonstrates that a cumulative benzene exposure of 400ppm years is equivalent to a mean annual exposure of 10ppm over a 40 year working lifetime. 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 currently impossible to predict 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 strict protective efforts may not completely prevent industrially-related benzene exposure and hematological cancers [7].

Levels of exposure and risk assessment

The issue of what is a safe level of exposure to benzene and what is not a safe level of exposure, or as some would like to define it sufficient exposure to cause a hematological cancer has been addressed by several studies and regulatory agencies. The study by the Environmental Protection Agency (EPA) as well as the International Agency for Research on Cancer [10] clearly indicates that there is no safe level of exposure to carcinogenic agents in the absence of epidemiological data of safety in humans. In the absence of safety studies in humans, experimental animal data must be applied from a policy and public health prevention point of view. Indeed, the American Petroleum Institute (API) stated that In as much as the body develops no tolerance to benzene and there is a wide variation in individual susceptibility, it is generally concluded that the only absolutely safe concentration for benzene is zero. Analysis of levels of exposure and risk assessment summarized by the 1998 position paper of the EPA clearly concludes that the dose-response relationship for benzene follows a linear line through zero.

The concept of cumulative benzene exposure for the working population must be well understood before one can address levels of exposure. They clearly show that diverse hematopoietic malignancies can develop at benzene exposure levels of less than 10ppm [11].

It is also important to remember that although many of the material safety data sheets of industrial solvents do not indicate the presence of benzene, the testimony in front of OSHA and the scientific papers published in that regards clearly indicate that industrial solvents contain benzene and cannot be produced without benzene contamination.

Benzene exposure levels are rarely available for most workers, because few workers are monitored for benzene exposure. The scientific medical literature allows the physician to extrapolate from the symptomatology of exposure, such as the threshold odor recognition for benzene, 61-91ppm, and symptomatology of dizziness, which is extrapolated to levels of 300ppm. This methodology has also been accepted by the U.S. Therefore it is imperative that the examining physician take a good history of exposure and look for odor recognition to extrapolate the levels of exposure and/or alternatively, symptoms of dizziness to extrapolate the levels of exposure. When history by the reporting physicians cannot be obtained, relying on depositions, job analysis and industrial hygienist assessment are acceptable [11].

Low Level Exposure To Benzene And Leukemia

genetic studies and markers and chromosomal change

The use of chromosomal abnormalities as a biological marker of exposure in humans have become an important tool in the research. Several abnormalities are found, including structural and numerical chromosomal aberrations, sister chromatoid exchanges (SCEs) and micronuclear changes. These are markers of changes in the cellular genetic materials, and represent damage induced by chemicals. These methodologies are viewed as cytogenetic assays, and by themselves cannot provide a diagnosis, but they complement other methodologies which include gene mutation analysis, and DNA changes. Among the

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important uses of cytogenetics as a biomarker is the relationship between chromosomal aberrations secondary to chemicals and carcinogeneses.

A patient who developed aplastic anemia after exposure to benzene, was shown to have significant chromatoid fragments. A cytogenic study which was carried out later, on a patient who developed leukemia after 22 years of continuous exposure to a high concentration of benzene, showed that later in the process there were changes in chromosomes in the bone marrow [12].

While it is true that these findings are in agreement with previous studies [13] they still could not explain the 43% of the patients who were not exposed, and still had abnormal chromosomal changes. This is a very important observation, since some investigators in the field claim that the Absence of chromosomal changes in benzene exposed individuals negates the clinical causative diagnosis of benzene induced hematopoietic disease. Essentially, all of the studies show that benzene can cause chromosomal changes, but does not cause perceptible changes in all patients, and the absence of visible chromosomal changes cannot and does not rule out the exposure to benzene as a causative factor. This is so because genetic point mutations and other types of changes are not observable using the standard cytogenetic banding techniques or even more sophisticated techniques such as fluorescence in situ hybridization (FISH), spectral karyotyping (SKY) or polymerase chain reaction (PCR) methods. Indeed, the courts have considered this issue and concluded that the genetic-chromosomal changes are not the equivalent of fingerprints of benzene exposure. The study by Zhang et al. [14] has examined chromosomal changes as a result of exposure to chemicals, such as benzene. Some leukemias have more typical chromosomal changes than others, but not all leukemias have typical chromosomal changes.

The study on the nature of chromosomal changes and benzene exposure was published by Luoping Zhang in Critical Reviews in Toxicology. The essence of this study is that benzene causes changes in certain chromosomes in certain hematological diseases. The absence of chromosomal changes does not rule out benzene exposure and benzene as a cause for the hematopoietic malignancy [14].

How to make or rule out a diagnosis of benzene-related hematological disorder

The examining physician who is faced with the question of causation in a patient with hematological malignancy and benzene exposure must utilize available epidemiologic and scientific data in the evaluation process. Ideally material safety data sheets as well as job descriptions and industrial hygiene reports, specifying the frequency and amount of exposure of benzene levels in the air should be considered, and the examining physician should request information in relation to other exposures such as solvent, radiation, pesticides, and cigarette smoking. Odour threshold recognition obtained via history, spills, headaches, and dizziness are scientifically extrapolated to levels of exposure. Although the latency period may be important in the final analysis, one must remember that the scientific literature shows a range of anywhere from 6 months with an average of 12 years and up to 40 years in some cases. In some instances, it is probable that both the exposure to benzene on an industrial basis and exposure to other toxic chemical on a nonindustrial basis are additive to causation. In that scenario the reporting physician must determine whether the exposure to benzene, regardless of the other exposures, was a substantial factor in the development of the patient's hematological cancer [14].

Conclusion

Benzene is a hematological carcinogen based on both experimental animal studies and human studies, as well as in vitro studies. While the precise mechanism of benzene carcinogenicity is not clear evidence that benzene metabolites damage DNA and chromofome, and in turn affects the stem cell: immature cell of the hematopoietic system which can in turn develop into any of the hematological cells originating from the bone marrow and the lymphatic system.

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