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Benzene-mediated hepato-toxicity: A review of the underlying mechanisms

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Abstract
Benzene is a substantial monocyclic aromatic hydrocarbon that serves as a feeder chemical in the production of lubricants, detergents, rubber, dyes, and insecticides in addition to serving as a solvent in a number of industrial and commercial operations. Through the working environment, a significant portion of the population is occupationally exposed to benzene. Chronic exposure to benzene causes a steady deterioration in haematological function and raises the risk of a number of diseases, such as leukaemia, aplastic anaemia, and myelo-dysplastic syndrome. There is some information that organic solvents, particularly benzene, might cause cell harm by releasing reactive oxygen species (ROS). Additionally, people exposed to organic solvents like benzene, which is characterised by reactive metabolic intermediates, may have a greater risk of cancer. Liver, peripheral blood and other tissues are all affected by benzophene, which can cause many enzyme activities to change. This can reduce the activity of antioxidant enzymes and cause oxidative stress, which is the imbalance between the rate at which reactive oxygen species (ROS) are produced and consumed by antioxidants. Four significant liver marker enzymes, including lactate dehydrogenase (LDH), Alkaline Phosphatase (ALP), alanine amino transferase (ALT), and aspartate amino transferase (AST), which are used to assess hepatotoxicity, are affected by benzene. By attaching to tissue protein, DNA, and RNA, benzene manifests its harmful consequences either directly or through its metabolites. Adenosine deaminase (ADA), a vital enzyme of purine metabolism, is affected by benzene in serum as well as the liver, where its activity is decreased after exposure to benzene. The purpose of this review is to determine the mechanistic basis of benzene's role in liver damage.

Keywords: Lubricants, detergents, rubber, dyes

Introduction
Benzene is an organic chemical compound with the molecular formula C6H6. The benzene molecule is composed of six carbon atoms joined in a planar ring with one hydrogen atom attached to each. Because it contains only carbon and hydrogen atoms, benzene is classed as a hydrocarbon (Paustenbach *et al*., 1993) [5]. One of the basic petrochemicals and a natural component of petroleum is benzene. Benzene is categorised as an aromatic hydrocarbon because of the cyclic continuous pi bonds that exist between the carbon atoms (Henderson, 1996) [2]. The scent of petrol is in part due to benzene, a colourless, extremely combustible chemical with a pleasant aroma. It is largely utilised as a precursor in the production of compounds with more complex structures, such as cumene and ethylbenzene, which are manufactured in annual amounts of billions of kilogrammes (Kalf & Snyder, 1987) [3]. Benzene is a significant industrial chemical, but due to its toxicity, it is rarely used in consumer goods.

Source of benzene
Benzene is formed from both natural processes and human activities. Natural sources of benzene include volcanoes and forest fires. Benzene is also a natural part of crude oil, gasoline, and cigarette smoke. Benzene is widely used in the United States (Aksoy, 1985) [1]. It ranks in the top 20 chemicals for production volume. Some industries use benzene to make other chemicals that are used to make plastics, resins, and nylon and synthetic fibers. Benzene is also used to make some types of lubricants, rubbers, dyes, detergents, drugs, and pesticides (Rinsky, 1989) [6].

Health Effects of Benzene

Acute exposure to benzene has toxic effects on the central nervous system; nevertheless, it is important to take into account benzene's myelotoxic, potential chromosome-damaging, and leukemogenic effects when assessing the chronic effects (Lv *et al*., 2007) [4]. Individual susceptibility varies greatly, as shown by the length of time needed for the development of chlorine benzene toxicity. The majority of reported cases of acute benzene intoxication occurred in individuals who were exposed to relatively high quantities of the chemical while working in less-than-sanitary settings (Ross, 2000) [7]. All cases of "Leukemia associated with benzene exposure" have probably all been caused by exposure to very high quantities of benzene and other chemicals.

Biomarkers of exposure

Several tests can determine exposure to benzene. Benzene itself can be measured in breath, blood or urine, but such testing is usually limited to the first 24 hours post-exposure due to the relatively rapid removal of the chemical by exhalation or biotransformation (Smith, 1996) [9]. Most people in developed countries have measureable baseline levels of benzene and other aromatic petroleum hydrocarbons in their blood. In the body, benzene is enzymatically converted to a series of oxidation products including muconic acid, phenylmercapturic acid, phenol, catechol, hydroquinone and 1, 2, 4-trihydroxybenzene (Sorahan *et al*., 2005) [10]. Most of these metabolites have some value as biomarkers of human exposure, since they accumulate in the urine in proportion to the extent and duration of exposure, and they may still be present for some days after exposure has ceased. The current ACGIH biological exposure limits for occupational exposure are 500 μg/g creatinine for muconic acid and 25 μg/g creatinine for phenylmercapturic acid in an end-of-shift urine specimen (Sorahan *et al*., 2005) [10].

Molecular mechanism

The paradigm of toxicological assessment of benzene is shifting towards the domain of molecular toxicology as it allows understanding of fundamental biological mechanisms in a better way. Glutathione seems to play an important role by protecting against benzene-induced DNA breaks and it is being identified as a new biomarker for exposure and effect (B. Zhang, 1996) [11]. Benzene causes chromosomal aberrations in the peripheral blood leukocytes and bone marrow explaining the higher incidence of leukemia and multiple myeloma caused by chronic exposure. These aberrations can be monitored using fluorescent in situ hybridization (FISH) with DNA probes to assess the effects of benzene along with the hematological tests as markers of hematotoxicity. Benzene metabolism involves enzymes coded for by polymorphic genes. Studies have shown that genotype at these loci may influence susceptibility to the toxic effects of benzene exposure. Individuals carrying variant of NAD(P)H: quinone oxidoreductase 1 (NQO1), microsomal epoxide hydrolase (EPHX) and deletion of the glutathione S-transferase T1 (GSTT1) showed a greater frequency of DNA single-stranded breaks (L. Zhang *et al*., 1999) [12].

Effects

The effects of acute exposure to high concentrations of benzene (neurological, dermal, respiratory, gastrointestinal) can be evident immediately after exposure. Neurological effects appear to be due primarily to the direct effects of benzene on the central nervous system. The anesthetic action of benzene on the central nervous system is similar to that of other anesthetic gases, first inducing excitation followed by depression, and if exposure continues, death through respiratory failure. Dermal, respiratory, and gastrointestinal effects are due to benzene's irritative properties (Sheets *et al*., 2004) [8].

Benzene is metabolized by the liver and its metabolites are excreted by the kidney. Benzene toxicity in large part is due to the generation of oxygen radicals via cytochrome P450. Benzene's water-soluble metabolites which are formed in the liver are responsible for its hematopoietic effects. Benzene can cause death in acute exposure primarily by its anaesthetic properties (respiratory arrest) or its myocardial sensitizing properties (fatal arrhythmias).

Children do not always respond to chemicals in the same way that adults do. In addition, children of different ages (e.g., in utero, infants, toddlers, older children) may have different responses to certain chemical exposures, and thus, different protocols for managing their care may be needed (Sheets *et al*., 2004) [8].

Toxicity

The radiomimetic nature of benzene and its ability to induce different sites of neoplasia indicate that formation of oxygen radicals is a major cause of benzene toxicity, which involves multiple mechanisms including synergism between arylating and glutathione-depleting reactive metabolites and oxygen radicals. Liver microsomes play an important role in the biotransformation of benzene whereas in the kidney, it produces degenerative intracellular changes. Cohort studies made in different countries suggest that benzene induces multiple myeloma in petrochemical workers. Drug-induced hepatotoxicity is an acute or chronic liver injury secondary to drugs or herbal compounds. It is difficult to diagnose because the presentation is similar to many hepatobiliary disorders. The principle treatment is the removal of the offending agent and close observation for resolution. Chronic Exposure

- Repeated exposure to high levels of benzene (200 ppm) can result in persistent CNS effects. Chronic benzene exposure in the workplace has been associated with hematologic disorders (i.e., thrombocytopenia, aplastic-anemia, pancytopenia, acute-myelgenous-leukemia).

References

1. Aksoy M. Benzene as a leukemogenic and carcinogenic agent. American Journal of Industrial Medicine, 1985, 8(1). [Start page]. https://doi.org/10.1002/ajim.4700080103.
2. Henderson RF. Species differences in the metabolism of benzene. Environmental Health Perspectives. 1996;104(Suppl. 6):[start page]. https://doi.org/10.1289/ehp.961041173.
3. Kalf GF, Snyder CA. Recent advances in the metabolism and toxicity of benzene. Critical Reviews in Toxicology, 1987, 18(2). [start page]. https://doi.org/10.3109/10408448709089859.
4. Lv L, Kerzic P, Lin G, Schnatter AR, Bao L, Yang Y, *et al*. The TNF-α 238A polymorphism is associated with susceptibility to persistent bone marrow dysplasia

following chronic exposure to benzene. Leukemia Research, 2007, 31(11). [start page]. https://doi.org/10.1016/j.leukres.2007.01.014.
5. Paustenbach DJ, Bass RD, Price P. Benzene toxicity and risk assessment, 1972-1992: Implications for future regulation. Environmental Health Perspectives. 1993;101(Suppl. 6):[start page]. https://doi.org/10.1289/ehp.93101s6177.
6. Rinsky RA. Benzene and leukemia: An epidemiologic risk assessment. Environmental Health Perspectives. 1989, 82. [start page]. https://doi.org/10.1289/ehp.8982189.
7. Ross D. The role of metabolism and specific metabolites in benzene-induced toxicity: Evidence and issues. Journal of Toxicology and Environmental Health - Part A, 2000, 61(5–6). [start page]. https://doi.org/10.1080/00984100050166361.
8. Sheets PL, Yost GS, Carlson GP. Benzene metabolism in human lung cell lines BEAS-2B and A549 and cells overexpressing CYP2F1. Journal of Biochemical and Molecular Toxicology, 2004, 18(2). [start page]. https://doi.org/10.1002/jbt.20010.
9. Smith MT. The mechanism of benzene-induced leukemia: A hypothesis and speculations on the causes of leukemia. Environmental Health Perspectives, 1996, 104(Suppl. 6). [start page]. https://doi.org/10.1289/ehp.961041219.
10. Sorahan T, Kinlen LJ, Doll R. Cancer risks in a historical UK cohort of benzene exposed workers. Occupational and Environmental Medicine. 2005;62(4):[start page]. https://doi.org/10.1136/oem.2004.015628.
11. Zhang B. Investigation of health status in workers exposed to low-level benzene. Zhonghua Yu Fang Yi Xue Za Zhi [Chinese Journal of Preventive Medicine], 1996, 30(3).
12. Zhang L, Rothman N, Wang Y, Hayes RB, Yin S, Titenko-Holland N, *et al*. Benzene increases aneuploidy in the lymphocytes of exposed workers: A comparison of data obtained by fluorescence in situ hybridization in interphase and metaphase cells. Environmental and Molecular Mutagenesis. 1999;34(4):[start page]. https://doi.org/10.1002/(SICI)1098-2280(1999)34:4<260::AID-EM6>3.0.CO;2-P.