BENZENE

Synonyms: benzol, cyclohexatriene.
Odor: characteristic strong aromatic odor.
Molecular weight: 78.11.
Molecular formula: C_6H_6.
TLV: 10 ppm; 30 mg m^{-3}.
Vapor pressure: 100 mmHg @ 20 °C.
Vapor density: 2.7 (air = 1).
Rat oral LD_{50}: 0.9–6.0 g kg^{-1}, depending on age and strain.
Acute toxicity: The characteristic pattern of acute benzene intoxication is stimulation of the central nervous system followed by respiratory depression, loss of consciousness and death.[1]
Human toxicity: Almost all studies of benzene exposure in humans are confounded by concomitant exposure to other solvents. Occupational exposure to benzene has long been associated with bone marrow depression and an increased incidence of blood dyscrasias, including leukopenia. lymphocytopenia, thrombocytopenia, pancytopenia, leukemia and lymphoma.' Lymphocytopenia has frequently been observed in individuals chronically exposed to benzene, and alterations in immune parameters have been reported along with benzene-induced lymphocytopenia.[2,3,4] The association of leukemia or lymphoma with chronic benzene exposure is documented by numerous case reports and retrospective studies.' Although the incidence of leukeniia varies significantly among various studies. it is not strikingly high. Aksoy *et al.*[5] reported an increased incidence of acute myelogenous leukemia in Turkish shoe workers chronically exposed to benzene. The annual incidence of leukemia was 13 per 100000, compared with 6 per 100000 in the general population. Alternatively. McMichael *et al.*[6] reported a twofold increase **in** the incidence of lymphatic leukemia in rubber workers chronically exposed to benzene. Other studies have found increased incidence of Hodgkin's lymphoma[7] and erythroleukemia[8] in individuals with a history of chronic benzene exposure.
Chronic toxicity: There is at present no convincing animal model for leukemia associated with benzene exposure. despite several attempts reported in the literature. This is due. in part, to a low incidence of leukemia as well as a lack of consistency among various studies. Ward *et al.*[9] observed no statistically significant increase in leukemia in male C57BL/6 mice administered a variety of subcutaneous doses of benzene for 54 weeks. Snyder *et al.*[10] reported an incidence for myelogenous leukemia of 2/40 in CD-1 mice chronically exposed to 300 ppm benzene. Maltoni and Scarnato'' recently reported the induction of Zymbal gland tumors (10 per 130) and an increased incidence of hemolymphoreticular (7 per 130 versus 1 per 130 in controls) and mammary gland tumors (11 per 130 versus 1 per 130) in Sprague Dawley rats repeatedly administered benzene in olive oil by gavage (50 or 250 mg per kg per day) for 52 weeks.

Numerous studies indicate that repeated exposure to benzene in mice, rats or rabbits results in a dose-liependent lymphocytopenia.[12,13,14] Repeated subcutaneous administration of benzene (44–660 mg per kg per day) to C57BL/6 mice for three days resulted in a depression of a variety of functional immune parameters ranging from decreased plaque forming-cell response to a loss of spleen cellularity." Tice *et al.*[16] observed a significant increase in the frequency of sister chromatid exchanges in bone marrow cells of CBA/2 mice following exposure to 3100 ppm benzene for 4 h. Bone marrow cell proliferation was inhibited, but no increase in the frequency of chromosomal aberrations was observed.

Benzene does not appear to be directly myelotoxic. but must be metabolized to form proximate toxic species. Benzene is oxidized via the mixed function oxidase system in liver with the formation of potentially reactive intermediates.[17] However, toxicity does not appear to be associated with cytochrome P-450 enzyme activity, but rather with osidation and conjugation pathways that presumably give rise to phenol and the polyhydroxylated metabolites of benzene.[18,19] Rickert *et al.*[20] and Greenlee *et al.*[21] demonstrated a relationship between benzene-induced lyniphotoxicity in rats and the concentration of the principal dihydroxy-metabolites. hydroquinone and catechol, accumulating in target tissues. Moreover, recent studies indicate that short-term intravenous or intraperitoneal administration of hydroquinone or catechol to C57BL/6 mice results in lymphocytopenia and suppression of a variety of immune functional responses similar to those encountered following benzene administration.[22]
In vitro studies: Morimoto and Wolff[23] observed an increase in the frequency of sister chromatid exchanges in human lymphocytes exposed to hydroquinone or catechol in culture. and Tunek *et al.*[24] identified hydroquinone as the principal metabolic intermediate responsible for the covalent binding of benzene in rat liver microsomes. Pfeifer and Irons[ZS] found that hydroquinone and its oxidation product. benzoquinone,. inhibited lymphocyte mitogenesis in culture at concentrations that did not produce cytotoxicity. These effects of lymphocyte blastogenesis were observed to be similar to those of known microtubule inhibitors and studies have, in fact, revealed these quinones to be potent inhibitors of microtubule assembly *in vitro*.[26,27]
Status: **A** proposal by OSHA to reduce the TLV for benzene from 10 ppm to **!** ppm was recently overruled by the US Supreme Court.

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