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Review Article

Hematotoxicity and Oxidative Stress Caused by Benzene

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Chronic benzene exposure results in progressive depression of bone marrow function, leading to a reduction in the number of circulating red and white blood cells. Epidemiological studies show that high-level occupational exposure to benzene results in an increased risk of aplastic anemia, acute myeloid leukemia, and chronic lymphocytic leukemia. Toxicity of benzene to be induced, it first must be metabolized to several metabolites which can accumulate in the bone marrow where they are further bioactivated by myeloperoxidases and other heme-protein peroxidases to reactive semiquinones and quinones, which lead to the formation of reactive oxygen species (ROS). ROS include superoxide radical anion, hydroperoxyl radical, hydrogen peroxide (H2O2), and the highly reactive hydroxyl radical. These species are generated by many physiological processes and can affect signal transduction cascades by altering the activities of certain protein kinases and transcription factors.

Key words: Benzene, Oxidative stress, Hematotoxicity.

INTRODUCTION

Benzene is one of the aromatic hydrocarbons, a colorless organic solvent derived from petroleum refining. Pure benzene is no longer widely employed in industries, but benzene-containing solvents, such as the extraction agent of vegetable oil and animal fat, and the solvents or thinners for rubber, resins, paints, and glues could be found as an industry production material. Occasionally, benzene-containing solvents are used as a degreaser for metal workpieces (Phillips and Johnson, 2001; Wong, 2002; Kuang and Liang, 2005). Benzene can be absorbed through the respiratory tract or via epidermal contact. Neglect of ventilation in the workplace and/or failure to use personal protective equipment when using benzene-containing solvents will increase the incidence of benzene poisoning (Kuang and Liang, 2005).

However, there are non-occupational exposures to benzene at gasoline stations and from individuals who smoke (Runion and Scott, 1985). It is a known human leukemogen, been linked to bone marrow depression, aplastic anemia, acute myeloblastic leukemia and acute nonlymphocytic leukemia (Aksoy *et al.,* 1972; Vianna and Polan, 1979; Yin *et al.,* 1987; Mikulandra et al., 1993; Sorahan et al., 2005) and even at low doses can affect white blood cell and platelet counts (Rinsky *et al.,* 1981; Ruiz *et al.,* 1993; Lan *et al.,* 2004). Benzene can also induce aplastic anemia and leukemia in mouse (Cronkite *et al.,* 1984; Lezama *et al.,* 2001; Chen, 2005) and rats (Heijne *et al.,* 2005; Macedo *et al.,* 2006) suggesting that it is exerting its effects in a similar manner.

Metabolism of Benzene

The chronic toxicity of benzene is the result of a series of biotransformation events that initiate with the generation of reactive intermediates. These compounds form covalent adducts with diverse critical macromolecules such as proteins and nucleic acids in liver, kidney, spleen, and blood (Snyder, 2004; Martinez-Velazquez *et al.,* 2006). Oxidation of benzene in the liver by cytochrome P450 2E1 (CYP2E1) to benzene oxide and other reactive intermediates is an initial step in the bioactivation of benzene and is a prerequisite for cellular toxicity (Snyder, 2002; 2004). Benzene oxide can be hydrolyzed by microsomal epoxide hydrolase (mEH) to benzene dihydrodiol that is then converted to a catechol or can undergo ring opening to produce *trans–transmuconaldehyde* or can spontaneously rearrange to form phenol, which is then hydroxylated in the liver to form hydroquinone (HQ) (Short et al., 2006). Once in the bone marrow, it is believed that HQ and catechol are converted by myeloperoxidase to 1,4-benzoquinone and 1,2-benzoquinone, respectively, which can be detoxified by reduction via NAD(P)H:quinone oxidoreductase-1 (NQO1) (Snyder, 2002 ; 2004).

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Benzene-induced cytotoxicity and genotoxicity

Benzene biotransformation produces numerous metabolites that can induce cytotoxicity and genotoxicity through diverse mechanisms (Smith, 1996; Valentine et al., 1996; Ross, 2000; Snyder, 2000; 2002; 2004; Recio *et al.,* 2005, Wan *et al.,* 2005, Sun *et al.,* 2014 and French *et al.,* 2015). These reactive metabolites include quinones that can bind to cellular macromolecules, including DNA, tubulin, histones and topoisomerase II. Benzoquinones and other benzene metabolites can cause oxidative DNA damage, lipid peroxidation in vivo, formation of hydroxylated deoxyguanosine residues and strand breaks in the DNA of bone marrow cells, implicating a role for reactive oxygen species (ROS) and covalent binding in benzene-induced toxicity. Formation of DNA double strand breaks (DSB) by ROS and other mechanisms can lead to increased mitotic recombination, chromosomal translocations and aneuploidy (Zhang *et al.,* 2002; Roma-Torres *et al.,* 2006, and Zhu *et al.,* 2013). Such genetic consequences may result in protooncogene activation, tumor suppressor gene inactivation, gene fusions, and other deleterious changes in stem cells that can ultimately result in leukemic responses (Wan *et al.,* 2005 and Kowalówka-Zawieja *et al.,* 2013).

Enzymes involved in benzene bioactivation and detoxication are key genetic determinants of benzene-induced cytotoxicity and genotoxicity. Valentine et al. (1996) ; Bauer et al. (2003) and Recio *et al.,* (2005) have used transgenic mouse models with inactivated alleles of genes that code for enzymes involved in the bioactivation and detoxication of benzene to identify critical pathways of biotransformation that lead to bone marrow cytotoxicity and genotoxicity. These animal models have demonstrated that CYP2E1 is a key enzyme involved in the initial steps of bioactivation to cytotoxic and genotoxic metabolites. Recio *et al.,* (2005) examined the impact of deficiency in two other enzymes involved in key steps of benzene bioactivation and detoxication, NQO1 and mEH, by using the inhalation route of exposure to benzene and genetically modified mouse models deficient in these enzymes.

The p53 DNA damage response is activated in the bone marrow in response to inhaled benzene (Boley *et al.,* 2002; Yoon *et al.,* 2003 and Hirabayashi *et al.,* 2004). Relative to wild-type (p53+/+) mice, p53+/− mice and p53−/− mice show a greatly attenuated expression of p53 transcriptional target genes involved in cell cycle control and apoptosis in the bone marrow, two important biological processes that regulate the response of this target tissue to benzene. In wild-type mice, benzene exposure induces the expression in mouse bone marrow of p21, gadd45, cyclins and bax, all hallmark genes of the p53 DNA damage response that is greatly reduced in p53 deficient mice(Boley et al., 2002; Yoon et al., 2003 and Hirabayashi et al., 2004). Faiola et al. (2004) have extended these studies by using gene expression profiling by microarrays and RT-PCR in enriched hematopoietic stem cells populations isolated from the bone marrow of benzene-exposed mice.

An additional metabolic pathway in which the benzene ring is opened also takes place in the liver. One of the major ring-opened metabolites are trans-muconaldehyde (MUC), a highly reactive dialdehyde diene (Latriano *et al.,* 1986). Metabolites of this compound including trans,transmuconic acid (MA) are detected in the urine of benzene treated animals and benzene-exposed humans (Grotz *et al.,* 1994; Zhang *et al.,* 1995), showing that the ring-opening pathway is utilized in vivo. The administration of MUC to mice at the same dose as that of benzene gives rise to similar toxic consequences and similarly leads to the excretion of MA (Witz *et al.,* 1985). MA has also been detected in the bone marrow, indicating that MUC or one of its metabolites is capable of reaching this site (Zhang et al., 1997).

However, because of its profound reactivity, MUC itself is not detectable in vivo following benzene administration, though it can be detected following in vitro microsomal metabolism of benzene (Latriano *et al.,* 1986; Grotz *et al.,* 1994; Zhang *et al.,* 1995 and Zhu *et al.,* 2013). MUC has been shown to be extremely hematotoxic in CD-1 mice (Witz *et al.,* 1985). At the cellular level, it can inhibit the maturation of erythroid cells in bone marrow (Snyder, 2000) and interferes with gap–junction intercellular communication (Rivedal and Witz, 2005). MUC causes formation of micronuclei in bone marrow cells (Oshiro *et al.,* 2001). As an α,β unsaturated carbonyl, it is very reactive, reacting with primary amines on protein and DNA. Although not strongly mutagenic in cell-based assays, MUC has been shown to give rise to DNA damage in a variety of cell lines, causing sister chromatid exchange (Witz *et al.,* 1990; Chang *et al.,* 1994 and saha *et al.,* 2012). It is cytotoxic, reacting with sulfhydryl groups leading to damage to proteins and enzymes (Witz *et al.,* 1985) and to the formation of DNA–protein crosslinks in cell lines (Schoenfeld and Witz, 1999). It can also react with glutathione in a Michael addition type reaction (Witz, 1989). In addition to its potent toxicity when administered to mice, MUC also exacerbates the toxic effects of the hydroxylated products of benzene (hydroquinone and benzoquinone) (Witz *et al.,* 1990).

Oxidative stress caused by benzene

As mentioned above, in order for benzene to exert toxicity, it first must be metabolized to several metabolites which can accumulate in the bone marrow where they are further bioactivated by myeloperoxidases and other heme-protein peroxidases to reactive semiquinones and quinones, which lead to the formation of reactive oxygen species (ROS). ROS include superoxide radical anion, hydroperoxyl radical, hydrogen peroxide (H2O2), and the highly reactive hydroxyl radical. These species are generated by many physiological processes and can affect signal transduction cascades by altering the activities of certain protein kinases and transcription factors (Droge, 2002).

In order to maintain proper cell signaling, it is likely that a number of radical scavenging enzymes maintain a threshold level of ROS inside the cell. However, when the level of ROS exceeds this threshold, an increase in ROS production may lead to excessive signals to the cell, in addition to direct damage to key components in signaling pathways. Oxidative stress occurs when the balance between ROS formation and detoxification favors an increase in ROS levels, leading to disturbed cellular function. ROS can also irreversibly damage essential macromolecular targets such as DNA, protein and lipids, which may initiate carcinogenesis (Imlay, 2003).

Evidence supporting a role for ROS in benzene-initiated toxicity includes studies showing that mice treated with benzene, phenol, catechol or hydroquinone, have elevated levels of oxidized DNA (Kolachana *et al.,* 1993 ; Faiola *et al.,* 2004 and Sul *et al.,* 2005), bone marrow cells from benzene treated mice have increased DNA binding activity for the transcription factor activator protein-1 (AP-1), a known target of oxidative stress (Ho and Witz, 1997) and studies demonstrating that benzene metabolites increase myeloid cell growth in vitro by the formation of ROS (Wiemels and Smith, 1999). While the role of bioactivation in benzene-initiated leukemia still remains unknown, these findings are consistent

with benzene-induced increased levels of ROS in target cells in leukemogenesis.

The studies of Winn (2003) and Wan *et al.,* (2005) had shown that the benzene metabolites phenol, hydroquinone, catechol and benzoquinone can increase the frequency of homologous recombination in vitro which was completely abolished by the antioxidative enzyme catalase. While homologous recombination is generally considered to be a repair mechanism, given the fact that it is not error-free, it is hypothesized that as the frequency of recombination increases so does the likelihood for erroneous repair, which can lead to genome instability and carcinogenesis. Furthermore, study of Wan *et al.,* (2005) had shown that hydroquinone or benzoquinone, but not phenol or benzene leads to an increase in ROS production in HD3 cells exposed to xenobiotic for 24 h as measured by 5- (and 6) -chloromethyl-2',7'-dichlorodihydrofluorescein. Addition of phenol with hydroquinone did not appear to further increase the production of ROS. Together, these data support a role for ROS in mediating benzene-initiated toxicity. ROS damage cellular macromolecules causing lipid peroxidation and nucleic acid and protein alterations. Their formation is considered as a pathobiochemical mechanism involved in the initiation or progression phase of various diseases such as atherosclerosis, ischemic heart diseases, diabetes, and initiation of carcinogenesis or liver diseases (Southorn and Powis, 1988; Hoffman *et al.,* 1989; Yagi, 1994 Halliwell and Gutteridge, 1999). Therefore, the concentrations of ROS have to be controlled by several defense mechanisms, which involve also a number of antioxidant and detoxifying enzymes.

Antioxidant enzymes play a crucial role in maintaining cell homeostasis. Their induction reflects a specific response to pollutants (Cheung *et al.,* 2001). Superoxide dismutase (SOD) is a scavenger of superoxide radicals that are converted to H2O2 (McCord and Fridovich, 1969). Glutathione peroxidase (GPx) is involved in the reduction of hydrogen peroxide, lipid hydroperoxides and other organic hydroperoxides (Tappel *et al.,* 1982). Glutathione-S-transferases (GST) represent a major group of detoxifying enzymes (Hayes and Pulford, 1995), which form a family of multifunctional proteins involved in the cellular detoxification of cytotoxic and genotoxic compounds and in the protection of tissues against oxidative damage (Mannervik and Danielson, 1988; Pickett and Lu, 1989). Besides certain roles in the endogenous metabolism, these enzymes are associated with the detoxification of xenobiotics such as drugs, carcinogens, and environmental pollutants in man and animals, and with pesticide and herbicide resistance in insects and plants (Hayes *et al.,* 1990).

Subchronic inhalation of mixture of cyclic hydrocarbons consists of benzene, cyclohexane, cyclohexanone to rats resulted in significant depression in glutathione peroxidase and glutathione-S-transferase activities in liver homogenate but no effects were noticed in superoxide dismutase nor TBRS levels in the study of Jr *et al.,* (2005). Some studies have shown, that GPx (Pigeolet *et al.,* 1990) and GST (Shen *et al.,* 1991) are inactivated by hydroperoxides, which exert their toxicity either directly by oxidation of SH groups of proteins or indirectly by hydroxyl radical's formation. It is known from literature that a significant number of the GST isoenzymes also exhibit GPx activity and catalyze the reduction of organic hydroperoxides to their corresponding alcohols (Prohaska, 1991 ; Mosialou *et al.,* 1993).

Hematotoxicity of benzene

Chronic benzene exposure results in progressive depression of bone marrow (BM) function, leading to a reduction in the number of circulating red and white blood cells (Snyder et al., 1975; Goldestain *et al.,* 1977). Epidemiological studies show that high-level occupational exposure to benzene results in an increased risk of aplastic anemia, acute myeloid leukemia, and chronic lymphocytic leukemia (Smith, 1996; US EPA, 1998; Snyder, 2000; Phibbs, 2001; Irons *et al.,* 2005; Maffei *et al.,* 2005; Roma-Torres *et al.,* 2006; Wang *et al.,* 2006, Chanvaivit *et al.,* 2007 and Takahashi *et al.,* 2012). Various studies have suggested that hematopoietic stem cells (HSC) are the target cells for benzene-induced alterations. In the BM, HSC are a small population (<0.05% of BM cells) of self-renewing, pluripotent cells that give rise to all blood cells (Morrisson and Weissman, 1994).

Enumeration of HSC can be performed by various in vivo and in vitro colony-forming assays. Inhalation exposure to benzene significantly reduced the number of transplantable spleen colony-forming units (CFU-S), granulocyte/monocyte colony-forming units (CFU-GM), and erythroid colony-forming units (CFU-E) in the bone marrow of male and female mice (Gill *et al.,* 1980; Cronkite *et al.,* 1982; Seidel *et al.,* 1989; Snyder, 2002, Faiola *et al.,* 2004 and Takahashi *et al.,* 2012), indicating a decrease in the number of HSC following exposure to benzene. Benzene was found to affect cell cycle kinetics as the fraction of CFU-GM in S phase was suppressed in male mice exposed to 300 ppm benzene for 2 weeks compared to unexposed control mice (Yoon *et al.,* 2001). In addition, persistent benzene-induced DNA damage was observed at an increased frequency of aneuploidy in the long-term self-renewing population of HSC (Lin−, c-kit+, Sca-1+) from male and female mice 8 months after gavage with benzene compared to the corn-oil-exposed control mice (Giver et al., 2001). Thus, benzene has short- and long-term deleterious effects on HSC.

In the study of Faiola *et al.,* (2004) bone marrow of mice exposed to benzene showed a significant reduction in the percentage of nucleated cells, pancytopenia, but there were no histological lesions of thymus. Irons *et al.,* (2005) described a novel form of bone marrow dysplasia in 23 workers exposed to high concentrations of benzene. Distinguishing features of benzene-induced dysplasia include: marked dyserythropoiesis, eosinophilic dysplasia and abnormal cytoplasmic granulation of neutrophilic precursors. Hematophagocytosis, stromal degeneration and bone marrow hypoplasia are also seen. Severe bone marrow dysplasia is frequently accompanied by clonal T cell expansion and alterations in T lymphocyte subsets. No clonal cytogenetic abnormalities were observed. They suggested that autoimmune-mediated bone marrow injury is an early or predisposing event in the pathogenesis of benzene-induced persistent hematopoietic disease.

The effects of phenol or hydroquinone administration on mononuclear leukocytes are detected even in stem cells in the bone marrow microenvironment and in distinct phases of maturation and proliferation (Li *et al.,* 1996; Pyatt *et al.,* 1998, 2000; Doepker *et al.,* 2000; Kalf, 2000; Smith *et al.,* 2000; Stillman *et al.,* 2000; Poirier *et al.,* 2002, McCue *et al.,* 2003 and Zhu *et al.,* 2013). The consequent reduced number and activity of B and T lymphocytes contribute to leukemia and immunosuppressive effects (Snyder, 2002, 2004). Conversely, phenol or hydroquinone may stimulate granulocyte production. Previous studies demonstrated an increase in the number of granulocyte-macrophage progenitor cells in the bone marrow of mice pre-treated with hydroquinone and an increased

proliferation of murine multipotent hematopoietic progenitor cells in vitro. Addition of phenol to hydroquinone generated even larger effects (Hazel *et al.,* 1996b). Furthermore, it has been shown in vitro that low concentrations of HQ induce terminal granulocytic differentiation in murine myeloblasts and inhibit apoptosis at the myeloblasts/myelocyte stage of differentiation (Hazel and Kalf, 1996 and Hazel *et al.,* 1996a).

The study of Macedo *et al.,* (2006) showed that hydroquinone exposure induced neutrophilia, probably because of a more intense mobilization of segmented cells from the bone marrow compartment. While it has been previously suggested that hydroquinone impairs production and/or maturation of granulocytes (Snyder, 2002, 2004), hydroquinone does not affect precursor cell numbers, but induces earlier maturation of neutrophils. In hydroquinone-exposed rats Macedo *et al.,* (2006) detected a significant reduction in the number of polymorphonuclear cells at the last phase of maturation in the bone marrow compartment and increased neutrophil numbers at the peripheral compartment. In contrast, phenol exposure did not alter any phase of cell maturation in the bone marrow compartment and did not modify the circulating number of leukocytes. These effects might be expected since phenol seems to act synergistically with hydroquinone or other phenolic compounds on granulocytic lineage alterations (Kolachana *et al.,* 1993; Moran *et al.,* 1996, Henschler *et al.,* 1996 and Zhu *et al.,* 2013).

Lezama *et al.,* (2001) subcutaneously injected 2 ml/kg (1940 mg/kg) benzene to CD1 male mice at either 5 days (successive) or 3 days (day after day) per week for a total of 10, 15, and 20 injections, respectively. Mice that received 15 and 20 injections at 5 day injections per week showed lethargy and irritability with 42% body weight loss and 68% spleen weight loss. Body and spleen weight losses were less severe (12% and 48%, respectively) in mice that received the same total injections but administrated at 3 days injections per week. Decreases in hemoglobin, erythrocytes, leukocytes, and BM cells ranged from 12% to 84%. While both injection schedules induced aplastic anemia. Inhalation of benzene vapor for 2.5 months induced aplastic anemia in Kunming mice with significant declines in erythroid progenitor cell counts and phosphoribosylpyrophosphate synthetase activity in colony-forming units (CFU)-erythroid. Treatment with a Chinese prescription, Sheng-Mai injection, brought erythroid progenitor cell counts and phosphoribosylpyrophosphate synthetase activity in CFU-erythroids to normal levels (Liu *et al.,* 2001).

Inhalation of various concentrations of benzene at 6 hours per day for 5 days caused the formation of phenylsulfate and phenylglucuronide to conjugate in the blood of Swiss mice. The reductions in spleen weight and white blood cell numbers correlated with the concentration of phenylsulfate in the blood (Wells and Nerland, 1991). Oral administration of benzene in rats resulted in decrease in total leucocyte count, lymphocytes, but no changes in red blood cells or hemoglobin in peripheral blood. Hitopathological examination of spleen detected decrease in the number of B-lymphocytes in the marginal zone (Heijne *et al.,* 2005).

Mechanism of benzene toxicity

In an attempt to understand the mechanism by which benzene produce bone marrow damage, several cellular targets of benzene metabolites have been identified. These include inhibition of spindle formation as a mechanism for inhibiting mitosis (Iron and Neptun, 1980), inhibition of the synthesis of interleukin 1, an essential factor in normal bone marrow function (Kalf *et al.,* 1996), covalent binding to proteins and DNA (Snyder, 2004), inhibition of DNA polymerase (Schwartz *et al.,* 1985), and chromosome damage (Zhang *et al.,* 2002). Although the impact of these and other possible effects may have differential significance in the development of benzene toxicity, all appear to occur in the course of development of benzene induced hemopathies. Benzene-induced chromosome damage has been the subject of considerable research and has benefited from a series of recent studies of workers exposed to benzene occupationally. The original study of Forni *et al.,* (1971) demonstrated gross chromosome aberration in benzene-exposed workers. Sasiadek (1992) reported that in benzene-exposed workers chromosomal breakpoints were observed primarily in chromosome 2,4 and 7. Zhang *et al.,* (2002) reported an aneusomy and long arm deletion of chromosome 5 and 7 in Chinese workers exposed to benzene, and Smith *et al.,* (2000) also observed translocation and aneusomy in chromosomes 8 and 21 in these workers.

It appears that myelodysplastic syndrome is a significant step in the generation of leukemia by benzene (Snyder, 2002). There are several mechanisms by which benzene metabolites might initiate carcinogenic response. Covalent binding to DNA to yield specific adduct formed by the reaction of hydroquinone with the bases guanine, adenine and cytosine. Because of two point attachment of the ring the result is the addition of a two ring system making the adduct bulkier than might be predicted from the addition of a single ring. Another mechanism which can alter DNA structure is the reaction of active oxygen species causing hydroxylation of specific bases. The most common of these is the formation of 8-hydroxyguanine, but hydroxylation products of adenine; thymine and cytosine have been reported (Sul *et al.,* 2005).

Rao and Snyder (1995) reported that the addition of hydroquinone, P-benzoquinone or 1,2,4-benzenetriol to HL-60 cells resulted in the production of superoxide and hydrogen peroxide. The generation of hydroxyl radical and singlet oxygen, which are hydroxylating species, would occur via Haber-Weiss chemistry. Rao (1996) suggested that benzene treatment resulted in the release of free iron from ferritin. He argued that iron is then chelated by either hydroquinone or benzenetriol which reacts with oxygen to generate reactive oxygen species. He suggested that glutathionylhydroquinone is a key intermediate in these reactions. It is, therefore, of interest to recall the suggestion of Brunmark and Cadenas (1988) that 2-OH-5-glutathionylhydroquinone may undergo auto-oxidation and oxidative recycling to yield superoxide. The further metabolism of superoxide via Haber-Weiss chemistry may well be enhanced in the presence of the iron chelate of 1,2,4 benzenetriol. The Brunmark and Cadenas (1988), and Rao (1996) postulates may come together to enhance the generation of the hydroxylating species, hydroxyl radical and singlet oxygen.

There has not been demonstration of either extensive covalent binding of benzene metabolites to bone marrow DNA nor of the large amount of 8-hydroxyguanine formation during benzene metabolism. However, Chen and Eastmond (1995) suggested that p-benzoquinone inhibits topoisoperase II, suggest that when DNA repair is inhibited the effect of low levels of DNA alterations may magnify. It may be assumed that early in the process of differentiation, at some point in the myeloid lineage a mutagenic event may not be manifested until differentiation reaches the myeloblast/myelocyte stage. Iron and Stillman (1996b), using CD34 cells, reported that hydroquinone enhanced clonogenic responses to GM-CSF.

Hazel and Kalf (1996), using 32D cells, reported that hydroquinone promoted cellular proliferation and differentiation

of the myeloblast to the myelocyte stage, but inhibited further maturation to the neutrophil. Normally the size of the myelocyte pool is controlled by the rate of myelocyte formation and the rate of maturation to neutrophils. When the number of myelocytes exceeds the need, some cells undergo apoptosis.

Hazel *et al.,* (1996) demonstrated that hydroquinone can also inhibit apoptosis thereby resulting in expansion of the clone of myelocytes. Any mutated cells in this population, which have not undergone DNA repair, will now proliferate, and in effect, promote the development of the leukemia. It may be that the example of benzene-induced promotion was observed in a study of Spalding *et al.,* (1999). Although large numbers of people have been exposed to benzene in the work place, often at the same or similar doses, there is wide variation in their response suggesting that there are factors which convey sensitivity to benzene may results from a series of polymorphisms in enzymes which modulate the production of toxic benzene metabolites, among those which may impact on benzene toxicity are polymorphism of CYP2E1 (Valentine *et al.,* 1996) activity because it is the major enzyme involved in benzene hydroxylation, the activity of conjugating enzymes of which glutathione transferase seem to be significant, and comparative activity of myeloperoxidase (Snyder, 2002), and reductase (NQ01) (Bauer *et al.,* 2003b).

Snyder (2000) suggests that individual susceptibility to benzene may be determined variability in these four sensitivity factors. Thus, high activity of CYP2E1 would increase the rate of formation of benzene metabolites and thereby render the individual more susceptible to benzene. However, depending upon the activity of the other three enzymes, the influence of any one of the other enzymes could be modulated. Thus, a high level of NQ01 might reduce the significance of high CYP2E1 and low GSH transferase in liver and low NQ01 coupled with high myeloperoxidase in bone marrow of an individual would render the person more sensitive than someone having the reverse level of enzymatic activity. Other factors relating to differentiation and maturation of cells in the bone marrow may also contribute to sensitivity to benzene.

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