pathways by analysis of urinary metabolites is not a feasible goal. Therefore, we have decided to forego analysis of tt-MA, and will utilize S-PMA and exhaled breath measurements as a monitor of benzene exposure.

27.3 Polymorphisms and Susceptibility to Benzene Toxicity

The role of genetic polymorphisms in conferring susceptibility to the development specific diseases and toxicity as a result of exposure to environmental agents is presently the subject of widespread interest. Genetic and phenotypic polymorphisms have been reported to coincide with increased susceptibility to benzene poisoning. Primary hydrolysis of benzene to phenol, hydroquinone and related hydroxy- metabolites in the liver is a requirement for toxicity, and the principal enzyme involved is cytochrome P-450 2E1 (CYP2E1) [33;35;36]. Hydroquinone and related hydroxy- metabolites are further oxidized in the bone marrow by myeloperoxidase (MPO) to benzoquinones which are thought to be the proximate toxic species [37;38;50]. The pattern of genetic polymorphisms in the human CYP 2E1 gene appears to be complex, subject to individual and ethnic variation, and it is unclear at present whether genetic polymorphisms affect expression or induction of CYP2E1 protein or enzyme activity [51]. CYP2E1 genetic polymorphisms have been reported not to impact the risk of BP in benzene-exposed workers; however, a phenotypic polymorphism in CYP2E1 hydroxylating activity has [50]. In light of the number and complexity of genetic polymorphisms at this locus, the analysis reported in the latter study cannot be considered to be definitive [50;51]. However, chlorzoxazone 6-hydroxylation has been demonstrated to selectively reflect CYP2E1 hydroxylating activity in vivo, and has been used to characterize a rapid and slow CYP2E1 phenotypic trait in a variety of populations [52-54]. The rapid hydroxylating phenotype has been reported to be associated with a 2.6-fold increased risk of BP [55]. Together, the combination of a rapid hydroxylating 2E1 phenotype and a homozygous mutation for the enzyme, NAD(P)H:quinone oxidoreductase 1 (NQO1) at base pair 609 has been reported to carry a 7.6-fold increased risk of BP compared to subjects who were slow hydroxylators and who carried one or two wild-type NQO1 genes [50]. Another evaluation of the potential association between P450 2D6 and 2E1 genotypes and risk of developing secondary or idiosyncratic AA proved negative [56].

NQO1 catalyzes the formation of hydroquinones from quinones without intermediate formation of semiquinone radicals [57]. Ross and coworkers first described a role for NQO1 in bone marrow stroma in detoxification of benzene in 1990 [58]. Subsequently, a homozygous mutation at position 609 in the NQO1 gene (C to T) has been described that leads to a lack of enzyme activity in vitro and in vivo (NQ01*2 allele) [59-61]. Moran et al have posited that this mutation results in the lack of enzyme induction in bone marrow stroma in response to oxidative stress [62]. Rothman and colleagues reported a 2.4 fold increased risk of BP in subjects exposed to benzene who were homozygous for the NQO1 609 mutation [55]. Alternatively, Larson and co-workers only observed a 1.4-1.6 fold risk of leukemia associated with the NQO1 609 polymorphism in patients receiving alkylating chemotherapy [63]. It is important to note that the NQ01*2 inactive allele is present at considerably higher frequency in Chinese populations (49%) than in Caucasians (16%) [64]. Independently, Naoe and colleagues have recently described a NQO1 polymorphism at codon 187 that is associated with an increased risk of treatment related AML (ser/ser) and an unexpected decreased risk of de novo AML (pro/ser) [65].