

Glutathione S-transferase theta 1 (GSTT1) catalyzes the conjugation of foreign compounds with glutathione and is thus thought to play an important role in the enzymatic detoxification of environmental carcinogens. Polymorphisms at this locus have been associated with an increased risk of ovarian cancer of specific histologic subtypes⁶⁶. At least seven independent studies have evaluated the influence of a homozygous deletion in GSTT1 on risk of developing MDS or AML⁶⁷. While two studies have observed an increased relative risk of MDS or AML associated with this polymorphism, five have not. The explanations for this apparent discrepancy are not well understood but may include ethnic differences in the study populations, the potential toxicity of glutathionyl-S-quinone, and/or inability to resolve associations with individual AML subtypes or cytogenetic lesions. One potentially important observation is a relatively large disparity in the number of s-AML's, including those with -5 and -7 cytogenetic findings, that were available for comparison among these studies. Therefore, it is important to investigate the role of GSTT1 polymorphisms focusing primarily on the development of s-AML in combination with detailed cytogenetic analysis.

A deficiency in MPO is well described that involves an underlying missense mutation leading to truncation of the resulting protein product. This leads to a failure in proteolytic cleavage which is a necessary step in post-translational modification of the enzyme⁶⁸. This deficiency in MPO is transmitted as an autosomal recessive and occurs at a frequency of about 0.05% in the general population^{69,70}. This mutation would theoretically serve to protect against benzene bone marrow toxicity.

In addition to these polymorphisms, weaker arguments can be made to investigate an even larger array of potential susceptibility genes. Due to limitations of time and scope, we have decided only to directly evaluate NQO1, CYP2E1 and GSST1. However, a basic strategy employed in all three of these studies is to provide a library of DNA material that can be made available for further studies, should resources and adequate scientific justification allow. Because of the importance of confirming the quantitative association previously reported for NQO1 (genotype) and CYP2E1 (phenotype) and the relative risk of developing BP, we propose to directly examine these two polymorphisms in a subset of workers occupationally exposed to benzene and to correlate these findings with hematologic and cytogenetic measures of effect. Further, this study design is particularly well suited to addressing outstanding questions with respect to the role of the GSST1 genetic polymorphism in leukemia risk, particularly s-AML. However, because MPO activates benzene metabolites a deficiency would be expected to confer relative resistance to BP, an outcome which would not be readily detectable in this study. Independently, MPO deficiency is commonly encountered as an acquired trait in cases of MDS and AML, suggesting that the feasibility of assessing a role for MPO in BP in these studies is extremely low.

27.4 Bone Marrow Metabolism and Toxicity

An established literature has accumulated to characterize the quantitative effects of benzene metabolites on functional and cytogenetic outcomes in human bone marrow and lymphoid cells in vitro^{17;25;42;44-46;71-79}. In many cases these events comport with prevailing theories on the pathogenesis of MDS and AML^{45;80}. Nevertheless, extrapolation of these studies to humans has been limited because of the lack of direct validation of the relationship between tissue metabolite