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In vivo mutagenicity of madder color and its constituents using gpt delta rats

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Madder color (MC) has been demonstrated to induce kidney and liver tumors in F344 rats. To explore the major cause in MC carcinogenesis, among many constituents, we have noted lucidin-3-O-primeveroside (LP) and its metabolites, lucidin and rubiadin (Rub) because of their genotoxicity. Additionally, since alizalin (Alz) has potential of oxidation, it was also considered to be a candidate agent despite lack of genotoxicity. In the present study, we examined reporter gene mutations in the kidneys of gpt delta rats given MC (5.0%), LP (0.08%), Rub (0.3%) or Alz (0.04%) in the diet for 8 weeks along with 8-hydroxydeoxyguanosine (8-OHdG) measurement. Significant increases in 8-OHdG levels were observed in all the treated rats except Rub-treated group. Gpt mutant frequencies (MFs) in rats treated with MC, LP and Rub were significantly elevated. Analysis of the mutation spectra revealed that increase in AT:TA transversion mutation was prominent in those groups in addition to some raise of GCTA transversion and GCTA transition mutations in all the treated rats. These results suggest that primary DNA damage induced by LP and its metabolites might participate in MC carcinogenesis together with Alz-induced oxidative DNA damage. In further studies, we will ascertain the effects of MC on gpt MFs in the liver, any other carcinogenic target site.

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Acrylamide and Glycidamide-induced gene mutations and mitochondrial gene expression profiles in transgenic mice.

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Acrylamide (AA) is a rodent carcinogen and its exposure can also cause degeneration in testicular tissue. The recent discovery of AA in a variety of fried and baked foods has drawn attention to its genotoxic effects in humans. Evidence suggests that glycidamide (GA), the epoxide metabolite of AA, is responsible for the genotoxic effects of AA. In order to evaluate the genotoxicity associated with AA and GA exposure in somatic and germinal tissues, groups of male and female Big Blue (BB) mice were administered 0, 100, or 500 mg/liter of AA or equimolar doses of GA in drinking water for 3-4 weeks. cII mutant frequencies (MFs) in the liver and testes and mitochondrial gene expression in the liver (only for higher doses) were conducted. Only high doses of AA and GA produced significant increases in the liver cII MFs compared to control MF (P<0.05). In testes, both the low and high doses of AA and GA induced 3-5 fold increase in the cII MFs compared to control MF (P<0.001). Molecular analysis of the mutants in the liver and testes indicated that AA and GA produced similar mutation spectra and that these spectra were significantly different from that of control (P<0.001). Mitochondrial gene expression using a newly developed and validated mouse Mitochip containing 542 mitochondrial genes showed a significant change in expression level of 76 mitochondrial genes with a false discovery rate of less than 0.05. However, GA did not seem to influence transcriptional level of mitochondrial genes. Interestingly, there was an A-mediated significant decline in transcriptional level of several 3-beta hydroxysteroid dehydrogenases that are involved in steroid biosynthesis. In addition, genes associated with complexes I, III, IV and V of oxidative phosphorylation were differentially expressed. These results suggest that exposure to AA and GA is genotoxic and that the significant down regulation observed in the expression of hydroxysteroid dehydrogenases may affect the endocrine function. Thus, these studies provide further insight into the genotoxic and mitochondrial mechanisms of AA and GA exposure in mice, which may be useful for human risk assessment.