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Effects of butylated hydroxyanisole on glutathione S-transferase activity and cyclophosphamide-induced teratogenicity

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Effects of repeated treatment with butylated hydroxyanisole (BHA) on the induction of glutathione S-transferases (GSTs) and teratogenicity of cyclophosphamide were investigated in rats. Pregnant rats were orally treated with BHA (50 mg/kg) for 7 days, from days 6 to 12 of gestation, and subcutaneously challenged with cyclophosphamide (15 mg/kg) 2 hr after the final treatment. On day 20 of gestation, the maternal and fetal abnormalities were examined. Separately, a part of rats was sacrificed for the assay of hepatic and placental GSTs activities on day 12 of gestation following 7-day treatment with BHA. Cyclophosphamide, administered on day 12 of gestation, induced 43.2% of fetal death and resorption, and 100% of malformations in live fetuses, in contrast to low fetal resorption (8.7%) and malformations (8%) in control group. The malformations include cranial defect and exencephaly (100%), micrognathia and tongue extrusion (100%), limb defects (40%), renal pelvic dilatation (39%), and cleft palate (15%). Interestingly, BHA induced GST activities by 62% and 46% over the control in liver and placenta, respectively, and remarkably reduced the fetal resorption (13.9%) and malformations, resulting in 62% of cranial defect and exencephaly, 68% of micrognathia and tongue extrusion, 29% of limb defects, and 14% of renal pelvic dilatation. Taken together, it is suggested that a long-term pretreatment with BHA could substantially prevent fetuses from

abortion and malformations following intrauterine exposure to teratogens including cyclophosphamide by inducing phase II antioxidant enzymes such as GSTs.