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The mouse rasH2/BHT model as an in vivo rapid assay for lung carcinogens.

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We have demonstrated the utility of a 9-week in vivo two-stage assay for lung cancer initiating agents, using transgenic mice carrying the human prototype c-Ha-ras gene (rasH2 mice) and butylhydroxytoluene (BHT) as a potent lung promoter (rasH2/BHT model). In the present study, to ascertain appropriate conditions for BHT administration in this model, the effects of exposure on proliferation of alveolar type II cells in male rasH2 mice were examined. Additionally, use of BHT was validated for promotion of urethane (UR) carcinogenesis in male and female rasH2 mice. In a time-course study of a single intragastric administration of BHT at a dose of 400 mg/kg, increased bromodeoxyuridine-labeling index (LI) reached a maximum 3 days after treatment and was still observed after 7 days. In a dose-response study, effects were dose-dependent, the dose of 400 mg/kg causing eight-fold elevation as compared to the control. With repeated administration, whereas the LI was increased dramatically at first, effects gradually diminished with further exposure, and finally six BHT treatments failed to induce cell proliferation. In a two-stage model using UR as the initiator, although up to five consecutive doses of BHT were able to exert continued enhancing effects in terms of adenoma yield, no increment was evident with further treatments. The data overall indicate that a rasH2/BHT model with five weekly administrations of BHT at a dose of 400 mg/kg is most efficacious.

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