CARCINOGENICITY AND MODIFICATION OF CARCINOGENIC RESPONSE BY ANTIOXIDANTS

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INTRODUCTION

Synthetic or naturally occurring antioxidants such as butylated hydroxyanisole (BHA), butylated hydroxytoluene (BHT), propyl gallate sodium L-ascorbate, and α-tocopherol have been widely used as food additives in various processed foods to prevent auto-oxidation of fatty acids. In addition, many naturally occurring antioxidants are present at appreciable levels in plants. In the light of studies which showed that antioxidants lack mutagenic activity and indeed even inhibit mutagenesis induced by carcinogens (13), they have been considered safe for use as food additives. In fact, since they have further been observed to inhibit chemical carcinogenesis in various organs when administered to rats concurrently with carcinogens (5,6,17), they have been considered as anticarcinogenic agents. However, BHA was recently found to be carcinogenic in the rat forestomach (9), and when antioxidants were given to rats after carcinogen exposure, they enhanced carcinogenesis in some organs while exerting an inhibitory influence in others (5-8). Therefore, antioxidants have both hazardous and nonhazardous effects in rodents, and by analogy also possibly in man.

This paper reports recent studies on the carcinogenic and modifying effects of synthetic and naturally-occurring antioxidants.

DOSE-RESPONSE STUDY OF BUTYLATED HYDROXYANISOLE IN RATS

Groups of 50 male F344 rats, initially 6 wk old (Charles River Japan, Inc., Kanagawa), were given an Oriental MF powdered diet (Oriental Yeast Co., Tokyo) containing BHA (>98% 3-tert-BHA and <2% 2-tert-BHA, Wako Pure Chemical Industries, Osaka) at levels of 0, 0.125, 0.25, 0.5, 1.0, or 2.0% for 104 wk. There was a significant decrease in final body weight compared with controls in all groups, except in those given 0.125% BHA in the diet. Table 1 shows the resultant incidences of proliferative

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Tab. 1. Proliferative and neoplastic lesions of the forestomach epithelium in F344 rats given diet containing BHA.

BHA in diet (%)	No. of rats[a]	No. of rats with lesions (%) Hyperplasia	Papilloma	Squamous cell carcinoma
0	50	0 (0)	0 (0)	0 (0)
0.125	50	1 (2)	0 (0)	0 (0)
0.25	50	7 (14)**	0 (0)	0 (0)
0.5	50	16 (32)***	0 (0)	0 (0)
1	50	44 (88)***	10 (20)**	0 (0)
2	50	50 (100)***	50 (100)***	11 (22)***

[a] Survived more than 50 weeks.

** $P < 0.01$, *** $P < 0.001$ vs control group

and neoplastic forestomach lesions. No squamous-cell carcinomas were induced at the 1.0% BHA level, although papillomas of the forestomach developed in 20% and 100% of the rats given a diet containing 1.0% and 2.0% BHA, respectively. The incidence of epithelial hyperplasia of the forestomach also increased with the dose of BHA, to 100% at the highest dose (10). These results thus demonstrated that the carcinogenic dose of BHA in rats is 2% in diet, and that a clear dose dependency exists regarding the development of hyperplasia and papillomas.

CARCINOGENICITY OF BUTYLATED HYDROXYANISOLE IN DIFFERENT SPECIES

Male F344 rats and male Syrian golden hamsters (Kagawa Tsuda Animal Farm, Kagawa) were given an Oriental MF pelleted diet containing 2.0% and 1.0% BHA, and male $B6C3F_1$ mice (Charles River Japan, Inc., Kanagawa) were treated with 1.0% and 0.5% BHA for up to 104 wk. The results are shown in Tab. 2. In rats, papillomas were induced in 75.5% and 91.5% of animals treated with 1% and 2% BHA, respectively, and carcinomas were again observed in the 2% group. Similar results were gained with hamsters, where the 1% level was also sufficient to induce malignant lesions. Although there were significant increases in the incidences of papillomas in mice given 0.5% and 1% BHA, the numbers of squamous cell carcinomas did not significantly differ from those observed in controls (15).

These results suggest that BHA is carcinogenic to rat and hamster forestomach epithelium, and that the respective carcinogenic doses are 2% and 1%. The data further indicate a possible weak carcinogenicity of BHA for mouse forestomach epithelium.