EVALUATION OF THE HEALTH ASPECTS OF BUTYLATED HYDROXYTOLUENE AS A FOOD INGREDIENT

JULY, 1973

Prepared for

Bureau of Foods
Food and Drug Administration
Department of Health, Education, and Welfare
Washington, D. C.

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Life Sciences Research Office
Federation of American Societies for Experimental Biology
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Bethesda, Maryland 20014
NOTICE

This report is one of a series of evaluations of the health aspects of the Generally Recognized as Safe (GRAS) food substances that are being made by the Life Sciences Research Office (LSRO) of the Federation of American Societies for Experimental Biology (FASEB) under contract with the Food and Drug Administration (FDA) of the U. S. Department of Health, Education, and Welfare. The Federation recognizes that the safety of GRAS substances is of national significance, and its resources are particularly suited to marshalling the opinions of knowledgeable scientists to assist in these evaluations. The Life Sciences Research Office, established in 1962 to make scientific assessments in the biomedical sciences, is conducting these studies.

Qualified scientists were selected as consultants to make a continuing review, analysis, and evaluation of the available information on each of the GRAS substances. These scientists, designated the Select Committee on GRAS Substances, were chosen for their competence and judgment with due consideration for balance and breadth in the appropriate professional disciplines. Members of the Select Committee on GRAS Substances who have contributed to this report are named in Section VII. The Select Committee's evaluations are being made independently of FDA or any other governmental or nongovernmental group.

These reports are approved by the Select Committee prior to submission to FDA. Although most LSRO consultants are members of FASEB constituent societies, the reports do not necessarily reflect the views of the Federation as a corporate body or carry the endorsement of the members of its constituent societies.

C. Jeffcarr, Ph.D., Director
Life Sciences Research Office
FASEB
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I. INTRODUCTION

Under terms of FDA Contract 72-85, FASEB's Life Sciences Research Office was requested to evaluate the health aspects of using butylated hydroxytoluene (BHT) as a food ingredient, primarily on the basis of information contained in four monographs furnished by FDA (1, 2, 3, 4), summarizing the world's scientific literature from 1920 through 1970, and in certain supplemental documents, including current literature citations obtained through Toxline* and Medline, * available as of July, 1973. BHT is a food substance that has been generally recognized as safe (GRAS) under the provisions of Section 121.101 of the Code of Federal Regulations (21 CFR 121.101, revised January 1, 1972).

As indicated in the Food, Drug, and Cosmetic Act [21 USC 321 (s)], GRAS substances are exempt from the requirement of the pre-marketing clearance for food additives. It is stated in 21 CFR 121.1 that GRAS means general recognition of safety by experts qualified by scientific training and experience to evaluate the safety of substances on the basis of scientific data derived from published literature. This section of the Code also indicates that expert judgment is to be based on the evaluation of results of credible toxicological testing, or for those substances used in food prior to January 1, 1958, on a reasoned judgment founded in experience with common food use, and is to take into account reasonably anticipated patterns of consumption, cumulative effects in the diet, and safety factors appropriate for the utilization of animal experimentation data. It is recognized further (21 CFR 121.3) that it is impossible to provide assurance that any substance is absolutely safe for human consumption.

The Select Committee on GRAS Substances of LSRO is making its evaluations of these substances in full recognition of the foregoing provisions. In reaching its conclusions on safety the Select Committee, in accord with FDA's guidelines, is relying primarily on the absence of substantive evidence of or reasonable grounds to suspect a significant risk to the public health, and realizes that a decision based on such

*Nationwide online bibliographic retrieval systems initiated by the National Library of Medicine, Bethesda, Maryland.
reasoned judgment, is expected even in instances where the available information is qualitatively or quantitatively limited. The Committee is also aware that biological testing, like all of science, is dynamic. Accordingly, the Committee's decisions, based as they are on the information now available, cannot anticipate and be guided by experiments not yet done or by the results of tests that may be reconducted, using new technologies that are constantly being evolved. These decisions will need to be reviewed as new or better information becomes available.

In this context, the LSRO Select Committee on GRAS Substances has reviewed the available information on BHT and submits its interpretation and assessment in this report, which is intended for the use of FDA in determining the future status of BHT under the Federal Food, Drug, and Cosmetic Act.

II. BACKGROUND INFORMATION

Butylated hydroxytoluene (BHT) is a white crystalline solid, prepared synthetically. Chemically it is \(2,6\)-di-\text{tert}-butyl-p-cresol and is closely related to the antioxidants butylated hydroxyanisole (BHA) and butylated hydroxymethylphenol. BHT is not known to occur naturally \(1,2,3,4\).

BHT is among several phenolic compounds that have been used in foods since 1949 because of their antioxidant properties. Most fats, oils and fat-containing foods are naturally susceptible to rapid rancidification and other oxidative reactions that produce compounds having objectionable taste and odor, making foods containing them unpalatable. Lipid oxidation is autocatalytic and proceeds as a complex of chain reactions the nature and speed of which vary with the substrate, temperature, light, availability of oxygen and the presence or absence of oxidation catalysts. Antioxidants like BHT act as "chain breakers" in the autoxidation processes under the usual conditions of processing, storage and use of fat-containing foods \(5\).

The Food Chemicals Codex specifies that BHT should contain not less than 99.0 percent \(C_{15}H_{24}O\). Maximum limits are specified for arsenic (3 ppm) and heavy metals as lead (10 ppm) \(6\).

BHT is used as an antioxidant in foods and in the packaging used for some foods, particularly those that contain oxidizable fats and oils,
in amounts ranging from 0.222 to 0.0001 percent in the following categories arranged approximately in decreasing order of BHT content: fats and oils, jams and jellies, sweet sauce, nut products, milk products (0.0046 percent), meat products, breakfast cereals, snack foods, soft candy, baked goods, confectionery frostings, gelatin puddings, frozen dairy products, gravies, alcoholic beverages, chewing gum, soups, processed vegetables, processed fruit, nonalcoholic beverages, and hard candy (7).

BHT was reported to be first used in food in the United States in 1949 (7). The total poundage of BHT used in foods in 1970 is reported to be twice that used in 1960 (7). However, there is no information now available to the Select Committee that permits it to determine the extent to which there has been significant change in the BHT content in any of the foregoing food categories over the past decade.

The Generally Recognized as Safe list indicates a tolerance for antioxidants, including BHT, of not over a total of 0.02 percent of the fat and oil content of the food (8). The meat inspection regulations of the U. S. Department of Agriculture place the same or lower limits for total antioxidants, including BHT, in some meat products (9).

III. CONSUMER EXPOSURE DATA

A National Research Council subcommittee has supplied the following information on the possible daily human intake of BHT in the total diet by individuals in various age groups (7). The Select Committee has converted these figures to possible intakes per kilogram of body weight.

<table>
<thead>
<tr>
<th>Age group</th>
<th>Possible daily intake</th>
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<tr>
<td></td>
<td>Total</td>
</tr>
<tr>
<td></td>
<td>Average: mg</td>
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<tr>
<td>0-5 mos.</td>
<td>0.5: mg</td>
</tr>
<tr>
<td>6-11 mos.</td>
<td>6.4: mg</td>
</tr>
<tr>
<td>12-23 mos.</td>
<td>8.1: mg</td>
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<tr>
<td>2-65+ yrs.</td>
<td>13.7: mg</td>
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*Calculations based on an average weight of 60 kg for an adult (10) and the following estimated weights of infants by age groups: 0-5 mos., 5 kg; 6-11 mos., 8 kg and 12-23 mos., 11 kg (11).
It is recognized that the figures calculated for the daily intake of BHT per kg of body weight in the age group 2–65+ years could be deceptively low, since individuals from age 2 to maturity will obviously weigh less than 60 kg; thus the daily intake of BHT per kg for a 20 kg child, for example, could be higher by a factor of 3 than the figures indicated in the table.

The NRC subcommittee has pointed out that its calculations of intakes of GRAS substances are overstated in most cases, often by considerable margins* (7). In the case of BHT, however, the intakes indicated in the foregoing table may be only slightly overstated. This is supported by the following calculation: NRC data show that the use of BHT for food purposes in the United States was 596,748 pounds or 271,249 kg in 1970. It is stated that this figure comprises between 60 and 70 percent of the total actual poundage used in food. On the basis of 60 percent adjusted to 100 percent (452,082 kg) and a U. S. population of 200 million, the per capita per day average intake would be 6.2 mg of BHT rather than 13.7 mg as given in the table.

In the light of these considerations the Select Committee concludes that the figures given in the foregoing table reflect a reasonable approximation of the actual levels of consumption of BHT by the several age groups.

An acceptable daily intake of the sum of BHT and BHA for man has been estimated by the Joint FAO/WHO Expert Committee on Food Additives to be 0.5 mg per kg body weight (unconditional) and 0.5–2.0 mg per kg body weight (conditional) (12). The term "conditional" means that the substance may be employed with an adequate margin of safety provided experts have reviewed the available evidence for the particular use. These figures approximate the consumption figures reported in the NRC consumer exposure data (7).

*An explanation for such overstatements is detailed in Section XI, "Significance and Use of Data in Safety Evaluations," of the NRC subcommittee's report (7). The Select Committee finds this explanation reasonable and concurs in the first recommendation in Section XII of the same report, that "In order to conduct a more accurate survey of the intake of substances used in food processing, food consumption data collected specifically for this purpose are needed."
IV. BIOLOGICAL STUDIES

After oral administration of a single dose of BHT to rats it was almost completely excreted within 4 days (13). It was also found that 20 to 40 percent of the administered dose was excreted in the urine and an additional 20 to 40 percent excreted in the feces. Since BHT is excreted in the bile, biliary excretion after absorption could account for much of the material in the feces. Extensive enterohepatic recirculation of BHT has been demonstrated in rats (14). Absorption and excretion studies have been carried out in man. Daniel et al. (15) administered 40 mg of BHT orally and found that about 67 percent of the material administered was excreted in the urine within 11 days. These data indicate that BHT is readily absorbed after oral administration in humans. However, it appears that no considerable enterohepatic circulation occurs in man.

The problem of tissue accumulation also has been investigated in the rat (13). Rats fed 0.5 to 1 percent BHT in a diet for up to 50 days were sacrificed and the BHT content of their fat and liver measured. It was found that only a small amount (less than 50 ppm) of BHT accumulated in the fat. These data demonstrate that BHT does not accumulate in fatty tissues. The half-life for stored BHT was 7-10 days in the rat. However, extracts of human adipose tissue contained from 0.15 to 1.30 ppm BHT; the compound was 5-6 times more concentrated in Americans than in Englishmen (16).

The metabolic fate of BHT has been studied in several animal species, including man. In general, the major metabolic products have been shown to be 3,5-di-tert-butyl-4-hydroxybenzoic acid, its glucuronide and S-(3,5-di-tert-butyl-4-hydroxybenzyl)-N-acetylcysteine (17, 18). Gilbert and Golberg (19) demonstrated that in the rat BHT retention is reduced after the induction of hepatic microsomal mixed-function oxidases. This enzyme system can be induced by prior BHT treatment and, therefore, it was concluded that animals subjected to prolonged BHT administration metabolize the substance at a higher rate. An enzyme that oxidizes BHT is induced in the liver by BHT ingestion. The reaction product is 2,6-di-tert-butyl-4-hydroxymethyl phenol (20).

It is noteworthy that an oxidation product of BHT, 3,3',5,5'-tetra bis-(tert-butyl) stilbenequinone, was found in cereal products and snack foods aged at elevated temperatures (21). This compound was found to be present in the range of 0.01 ppm in such foods after aging but no data were presented concerning its metabolism or toxicology.
The oral lethal dose and \( \text{LD}_{50} \) of BHT in various animal species have been reported. In the rat, the \( \text{LD}_{50} \) is 1.7 and 2.0 g per kg in males and females, respectively. In the rabbit, the lethal dose is greater than 2 g per kg and in the guinea pig, the lethal dose is approximately 10.7 g per kg (22). Other investigators have reported the oral \( \text{LD}_{50} \) of BHT in rats, mice, rabbits and hamsters to be 2250, 1800, 3200, and 2820 mg per kg, respectively (23).

Short-term toxicity studies have been carried out with BHT by a number of investigators. BHT has been fed to dogs at levels of 170 to 940 mg per kg per day for 12 months and to rats at a level of 0.2 percent in the diet for 90 days (22) with no discernible toxic effects. Rats fed 0.1 and 0.5 percent BHT in the diet for 6 months or less exhibited significant reduction in the growth rate of male animals only when the BHT was incorporated in a diet supplemented with 20 percent lard (24). These investigators also observed an increased incidence of alopecia in rats fed 0.5 percent BHT in the diet. This effect could only be observed when the BHT was fed in lard; the response was not manifested in rats fed BHT in coconut oil. Even at a dietary level of 0.5 percent, BHT had no effect on one reproductive cycle in the rat and no effect on the histology of spleen, kidney, liver, testes, or skin. However, there was significant increase in the weight of the liver relative to body weight and the mean absolute weight of the liver was also increased.

Several other investigators have noted that the administration of BHT affects liver weight. Hepatomegaly, accompanied by increased proliferation of the smooth endoplasmic reticulum and by increased mitotic activity, was observed in rats fed 2.8 mg BHT per calorie of diet for 22 of 24 days; another group of rats received 1.4 g per kg body weight as a single dose (25). This effect seemed to occur at about 200 times the acceptable dose (0.5 to 2.0 mg per kg) estimated by FAO/WHO (12). In doses of 150 to 300 mg per kg per day, there was an increase in absolute and relative liver weights in the rat (26). The same authors showed that at 0.5 percent BHT in the diet for 10 days there was an increase in liver weight but no statistically significant increase when the dietary level was 0.5 percent for 8 weeks.

In recent work young rhesus monkeys administered 500 mg of BHT in corn oil per kg daily by gastric intubation for 4 weeks showed no clinical abnormalities but exhibited liver hypertrophy, proliferation of hepatic endoplasmic reticulum, and nucleolar fragmentation in many of the hepatic nuclei. The observed effects were less pronounced with BHT than with BHA at the same dosage. At doses of 50 mg per kg,
hepatic cytoplasmic changes were less obvious and no nucleolar changes were observed (27). No significant effect was observed on a number of organ weights, including the liver, in rats fed 0.5 percent BHT (22). No evidence of hepatotoxicity was found in rats fed 0.1 percent BHT for 16 weeks (28). A consistent no-effect level with respect to liver enlargement of 25 mg per kg per day of BHT in rats has been reported (19).

Since there is little doubt that BHT increases the liver weight of animals fed adequate doses of BHT in their diet, it can be expected that this effect can be evaluated with biochemical measurements. It has been demonstrated that, in addition to liver weight, total protein and ribonucleic acid increased in the livers of rats fed 0.5 percent BHT in the diet for 68 days (29). Mixed function oxidases in the microsomes of liver obtained from animals fed BHT have also been shown to have increased enzyme activity. The synthesis of drug-metabolizing enzymes is induced (30, 31). Biphenyl 4-hydroxylase activity was increased at concentrations of BHT that did not increase liver size (32). Cytochrome oxidase activity of liver tissue decreased 20 percent when BHT was fed to rats at the 0.5 percent level for 10 days (26). BHT at a level of 500 mg per kg per day had a striking effect on ascorbic acid excretion; this condition remained elevated for 1 week after dosage of BHT was ended (26). Increase in liver weight and depression in glucose-6-phosphatase activity were no longer manifest after a 14-day recovery period following cessation of administration of BHT (33). But, whereas liver weight returned to normal within two weeks of maximum drug effect in rats, other parameters such as elevated DNA content, number of liver cell nuclei, and percentage of tetraploid nuclei remained relatively constant over a 7-week post-treatment period (34). Takanaka et al. (35) fed BHT to rats at levels of 50 to 150 mg per kg per day and observed that at the high doses BHT increased liver weight but at the low dose there was no such increase in weight but a substantial increase in activity of drug metabolizing enzymes, aminopyrine N-demethylase, hexobarbital hydroxylase, and butynamine N-demethylase \((C_{10}H_{19}N\cdot HCl)\). There was no direct relationship between increase in activity of the drug metabolizing enzymes and increase in liver weight. The increased drug metabolizing activity induced by feeding BHT was reflected in reduction of the activity of pentobarbital by about 60 percent.

The consensus is that the effect of BHT on liver enlargement represents a type of hypertrophy, which is fully reversible and without toxicological significance. However, a somewhat different view notes that increases in liver size and increases in drug-metabolizing enzymes can be interpreted as an adaptive mechanism (36). With
two substances other than BHT it has been demonstrated experimentally that a point is reached when adaptation fails, a new condition develops, and injury commences (37). It does not appear that "fully adapted" livers have been challenged by additional doses of BHT or, more importantly, other chemicals. Such information should be available before one can conclude that BHT-induced liver hypertrophy is completely harmless.

The induction of hepatic microsomal enzymes is an established effect of BHT. The pharmacological implications of microsomal enzyme induction have been described (38). Others have discussed the role of microsomal hydroxylases in polycyclic hydrocarbon carcinogenesis (39, 40). It is also apparent that microsomal enzymes can be induced in such tissues as the intestinal tract, lung, adrenals and kidney. The effects of BHT on these extra-hepatic systems have not been reported. While probably the overall contribution of these sites to the metabolism and disposition of foreign substances is small, the effects of microsomal enzyme induction in these tissues, exposed to potentially carcinogenic substances, are unknown. There are observations indicating that aryl hydrocarbon hydroxylase is responsible for the conversion of some polycyclic hydrocarbons to toxic and carcinogenic forms (41). It is also known that the mixed-function oxidases in the microsomes can affect the metabolic transformation of steroid hormones. BHT may stimulate, as do other microsomal enzyme inducers, the activity of steroid hydroxylating enzymes (26). Such stimulation could affect reproduction.

BHT has been shown to influence lysosomal membranes and these data are of interest as related to the role of lysosomes in physiologic and pathologic processes (42). However, before any interpretation of the data concerning the effects of BHT on lysosomes can be attempted, it must be pointed out that in the study in question (42) too few animals and too many dose schedules were employed. No conclusions ought to be drawn before these experiments have been validated using more appropriate numbers of animals and experimental conditions.

It has been reported recently (43) that in large doses administered parenterally BHT is capable of producing lung damage in mice. Histological examination of lung tissue revealed thickened intra-alveolar septa, congestion, and a general pattern of tissue disorganization; the lesions seemed to be dose-dependent and appeared to be reversible. Alterations in the lung were generally observed at a threshold dose of 40 mg per kg.
These data await confirmation from studies by other investigators. However, it is interesting to note that similar pulmonary changes have been found in dogs fed 1.4 - 4.7 g BHT per kg per day for 28 days (22). These investigators interpreted their finding as not being due to BHT, but rather to the way the animals were killed (by air embolism). This explanation cannot be substantiated without further investigations on the eventual effects of BHT on lung tissue.

Long-term feeding studies have been carried out in several species. Rats maintained on diets containing up to 1 percent BHT for 2 years exhibited no evidence of pathology and carcinogenicity (22). Mice have been fed 0.5 percent BHT in the diet for 28 months (44); no pathology was observed. Rats maintained on 0.1 percent BHT in coconut oil for 2 years exhibited no differences between control and experimental animals (24).

BHT had no clearly discernible effect on nidation or maternal or fetal survival when administered in daily amounts up to 180 mg per kg (day 6 through day 15 of gestation) in mice, up to 225 mg per kg (day 6 through day 15 of gestation) in rats, and up to 280 mg per kg (day 6 through day 10 of gestation) in hamsters (45).

A multigeneration study in rats fed 300, 1000, and 3000 ppm BHT in their diet has been conducted (46). Females were mated at 100 days with males maintained on the same regimen. Observations included complete blood counts, cell indices, reticulocyte count, prothrombin time, serum glutamic-pyruvic transaminase, serum glutamic-oxaloacetic transaminase, fasted blood sugar, serum alkaline phosphatase, blood urea nitrogen, icterus index, urine albumin, reducing substances and microscopic elements, organ weights of liver, kidney, spleen, gonads, heart, brain, thyroid and adrenal, and microscopic pathologic studies of heart, trachea, lungs, liver, pancreas, stomach, small intestine, caecum, colon, spleen, cervical and mesenteric lymph nodes, kidney, urinary bladder, testes, ovaries, prostate, uterus, pituitary gland, submaxillary gland, thyroid, parathyroid, adrenals, skeletal muscle, bone marrow of sternum and femur, sciatic nerve, brain, seminal vesicles, esophagus, and spinal cord. These tests were conducted on animals of the first and second generations. The investigators found that at a level of 3000 ppm of BHT the growth rates of parents and young were depressed 10 to 20 percent. They also found a 20 percent increase in serum cholesterol level after 28 weeks, but no elevation after 10 weeks, and a 10 to 20 percent increase in relative liver weight after 42 weeks. All other observations at 3000 ppm and all observations at 1000 and 300 ppm were comparable with those of the controls.
All criteria of reproduction were normal and no teratogenic effects were detected. They suggest that by all criteria in 2 generations of rats and their offspring, a "no-effect" level of 1000 ppm BHT in a high fat diet is established.

Feeding tests with mice and rats demonstrated no evidence of significant embryo toxicity in doses of 1000 mg per kg as a single dose on a specific day of pregnancy or up to 750 mg per kg in daily doses both before and during pregnancy. Observations included mating and fertility indices, number of corpora lutea, implantation and resorption sites, and examination of fetuses for gross skeletal and soft tissue abnormalities (47). In another report (48) the investigators were unable to demonstrate any effect on fertility index, litter size or viability index in rats fed 0.125 to 0.313 percent BHT in the diet while 1.55 percent caused drastic weight loss or fetal deaths. No effect on one reproductive cycle of the rat was observed but anophthalmia was noted in the young of rats fed BHT at levels up to 0.5 percent of the diet (equivalent to 250 mg per kg) of body weight (48). One of these investigators (49) as well as another laboratory (47) were unable to repeat these results in subsequent studies. It was suggested by the latter (47) that the original observations (24) may have been due to avitaminosis A rather than to the feeding of BHT. BHT fed in a single dose of 0.5 g in the diet after mating was reported to have definite prophylactic value in reducing the frequency of resorptions in the rat (50).

The possible mutagenic effects of BHT have been tested (51). BHT did not produce any measurable mutagenic response or alteration in the recombination frequency for Saccharomyces cerevisiae in either the host-mediated assay or the associated in vitro tests. BHT exhibited no adverse effect on metaphase chromosomes from rat bone marrow in the treatment range of 30 to 1400 mg per kg for 6 to 48 hours. BHT caused a sharp increase in the percentage of aberrant human embryonic lung cells in tissue culture in the range of 2.5 to 250 µg per ml. No consistent responses occurred to suggest that BHT is mutagenic in the rat as measured by the dominant lethal gene test. Intraperitoneally administered BHT in a dose of 1000 mg per kg also failed to indicate mutagenicity by a dominant lethal test in mice (52).

Monolayers of monkey kidney cells have been exposed to concentrations of BHT varying from 0.1 mM to 0.136 mM (53). Inhibition of cell multiplication and a substantial depression of the incorporation of radioactive precursors into DNA, RNA and protein were observed.
However, both effects were reversible and no morphological alterations in the structure of the exposed cells were observed. At concentrations up to 30 mg of BHT per g of cells, no visible cytopathological changes were observed. Another laboratory has stressed the point that inhibition of cell multiplication was fully reversible and could be repeated several times in the same monkey kidney cell culture (54). It was concluded that the effect of BHT on the incorporation of precursors into macromolecules was not a specific effect of BHT and that the effects occur only at rather high concentrations of BHT in the culture medium. It is not established to what extent tissue culture techniques can be used to evaluate or to predict toxicity (55). Therefore, the effects of BHT in tissue culture cannot be interpreted at this time.

No reports of studies of the carcinogenicity of BHT have been found but there are reports suggesting that BHT interferes with the induction of tumors in two strains of rats by p-dimethylaminobenzylidene (56), and that BHT suppresses the processes of protein and nucleic acid biosynthesis in cancer cells in vivo in mice with Ehrlich's ascites carcinoma and solid hepatoma 22 (57).

Allergies to BHT in food have not been reported.

V. OPINION

The information on the metabolism and toxicology of butylated hydroxytoluene (BHT) is extensive. There is ample evidence of efficacy of this compound as an antioxidant. It has been suggested that BHT in fatty tissue may even have some effect similar to that of vitamin E (58). There are some data to indicate that BHT in diets reduces the incidence of certain tumors and the rate of fetal absorption in the rat.

The available evidence does not support the view that BHT interferes in any specific way with cellular metabolism. There is no evidence that demonstrates that BHT causes frank biochemical lesions in the liver; moreover, it is obvious that high doses of BHT are needed to induce biochemical alterations. With 0.1 percent BHT in the diet in rats there are differing data in the literature concerning the effect of such treatment on liver growth and liver enzymes. At 0.05 percent in the diet, no toxic effects are discernible. This "no-effect level" is equivalent to 50 mg per kg per day.
However, BHT increases the level of microsomal enzymes in the liver. The significance of this increase raises certain questions. The liver weight of animals fed BHT is increased and some interpret this enlargement as hypertrophy which is fully reversible and without apparent toxicological significance. But a point could occur at which adaptation fails, a new condition is created, and injury commences. It does not appear that "fully adapted" livers have been challenged by additional doses of BHT or, more importantly, other chemicals. In view of the widespread use, for example, of oral contraceptives, it is felt that information should be available on the effect of challenging fully adapted livers with compounds which are themselves metabolized by microsomal hydroxylases. Therefore, there is the need to determine the effects of BHT at levels now present in foods under conditions where steroid hormones or oral contraceptives are being ingested.

Other tissues such as lung and the gastrointestinal mucosa, in addition to liver, can respond to enzyme inducing agents. More information is required on the inducing properties of BHT on extra-hepatic organs. If induction should be found to occur, it would be necessary to determine the effect of such enzymes on the conversion of other ingested materials into toxic substances or carcinogens.

The Select Committee has weighed the foregoing and concludes that:

While no evidence in the available information on butylated hydroxytoluene (BHT) demonstrates a hazard to the public when it is used at levels that are now current and in the manner now practiced, uncertainties exist requiring that additional studies should be conducted.
VI. REFERENCES CITED


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41. Miller, Sanford A. Unpublished data.


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September 12, 1973
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