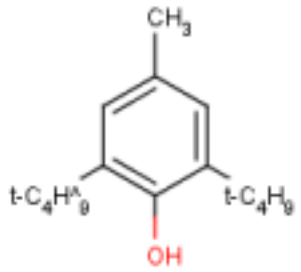
BUTYLATED HYDROXYTOLUENE

SYNONYMS

"Ionol" CP-antioxidant
1-Hydroxy-4-methyl-2,6-di-tert-butylbenzene
2,6-Bis(1,1-dimethylethyl)-4-methylphenol
2,6-Di-t-butyl-4-methylphenol
2,6-Di-t-butyl-p-cresol
2,6-Di-terc.butyl-p-kresol
2,6-Di-terc.butyl-p-kresol [Czech]
2,6-Di-tert-butyl-1-hydroxy-4-methylbenzene
2,6-Di-tert-butyl-4-cresol
2,6-Di-tert-butyl-4-hydroxytoluene
2,6-Di-tert-butyl-4-methylhydroxybenzene
2,6-Di-tert-butyl-4-methylphenol
2,6-Di-tert-butyl-p-cresol
2,6-Di-tert-butyl-p-methylphenol
3,5-Di-tert-butyl-4-hydroxytoluene
4-Hydroxy-3,5-di-tert-butyltoluene
4-Methyl-2,6-di-terc. butylfenol
4-Methyl-2,6-di-terc. butylfenol [Czech]
4-Methyl-2,6-di-tert-butylphenol
4-Methyl-2,6-tert-butylphenol
AI3-19683
AO 29
AO 4
AO 4K
AOX 4
AOX 4K
Advastab 401
Agidol
Agidol 1
Alkofen BP
Antox QT
Antrancine 8
BHT 264
BUKS
Butylated hydroxytoluene
Butylated hydroxytoluol
Butylhydroxytoluene
Butylohydroksytoluenu
Butylohydroksytoluenu [Polish]
CAO 1
CAO 3
CCRIS 103
Caswell No. 291A
Catalin antioxydant 1
Catalin cao-3
Chemanox 11
DBPC

DBPC (technical grade)
Dalpac
Deenax
Di-tert-butyl-p-cresol
Di-tert-butyl-p-cresol (VAN)
Di-tert-butyl-p-methylphenol
Dibunol
Dibutylated hydroxytoluene
EPA Pesticide Chemical Code 022105
HSDB 1147
Impruvol
Ionol
Ionol (antioxidant)
Ionol 1
Ionol CP
Ionole
Kerabit
NCI-C03598
NSC 6347
Nocrac 200
Nonox TBC
P 21
P21
Parabar 441
Paranox 441
Phenol, 2,6-bis(1,1-dimethylethyl)-4-methyl-
Stavox
Sumilizer BHT
Sustane
Sustane BHT
Swanox BHT
Tenamen 3
Tenamene 3
Tenox BHT
Tonarol
Topanol
Topanol O
Topanol OC
Toxolan P
UNII-1P9D0Z171K
Vanlube PC
Vanlube PCX
Vianol
Vulkanox KB
o-Di-tert-butyl-p-methylphenol

CHEMICAL STRUCTURE



CHEMICAL FORMULA

$C_{15}H_{24}O$

IDENTIFIER DETAILS

CAS Number	:	128-37-0
CoE Number	:	-
FEMA	:	2184
EINECS Number	:	204-881-4
E Number	:	E321

SPECIFICATIONS

Melting Point: 71 °C

Boiling point: 265 °C

STATUS IN FOOD AND DRUG LAWS

CoE limits:

Beverages (mg/kg)	Food (mg/kg)	Exceptions (mg/kg)
-	-	-

Acceptable Daily Intake:

ADI (mg/kg)	ADI Set by	Date Set	Comments
0 to 0.3 mg/kg	JECFA	1995	-

FDA Status:[CFR21]

Section Number	Comments
172.115	Food additives permitted for direct addition to food for human consumption.
175.105	Indirect food additives: adhesives and components of coatings.
176.210	Indirect food additives: paper and paperboard components.
177.2600	Indirect food additives: polymers.
181.24	Prior-sanctioned food ingredients.

HUMAN EXPOSURE

Natural Occurrence: Butylated hydroxytoluene (BHT) does not occur in nature.

Reported Uses: Butylated hydroxytoluene (BHT) is a lipophilic (fat-soluble) organic compound that is primarily used as an antioxidant food additive (E number E321). In addition, BHT is used in cosmetics, pharmaceuticals, jet fuels, rubber, petroleum products, and electrical transformer oil.

TOXICITY DATA

This ingredient has been registered under REACH. Under REACH, registrants have an obligation to provide information on substances they manufacture or import. This information includes data on hazardous properties (covering various toxicological endpoints), guidance on safe use and classification and labelling. The European Chemicals Agency (ECHA) makes this information publicly available on its website: http://echa.europa.eu/.

In vivo toxicity status

Carcinogenicity and mutagenicity

A bioassay of BHT for possible carcinogenicity was conducted by the NTP (1979) by administering the test chemical in feed to F344 rats and B6C3F1 mice. Groups of 50 rats and 50 mice of each sex were administered BHT at one of two doses, either 3,000 or 6,000 ppm; the rats for 105 weeks and the mice for 107 or 108 weeks. Matched controls consisted of 20 untreated rats and 20 untreated mice of each sex. All surviving animals were killed at the end of administration of the test chemical. Mean body weights of the dosed rats and mice were lower than those of the corresponding controls and were dose related throughout most of the bioassay. Survival was not affected significantly in the dosed groups of rats or mice, and the survival was 60% or greater in all dosed or control groups of rats and mice of each sex at the end of the bioassay. A sufficient number of animals were at risk for the development of late-appearing tumours. Alveolar/bronchiolar carcinomas or adenomas occurred in the female mice at a significant incidence in the low-dose group (P=0.009) but not in the high dose group, and the incidences were not significantly dose related (control 1/20, low-dose 16/46, high-dose 7/50). Thus, these lung tumours in the female cannot clearly be related to the administration of the BHT. No tumours occurred in either male or female rats at incidences that were significantly higher in dosed groups than in corresponding control groups. Nonneoplastic lesions that may have been related to the administration of the test chemical included focal alveolar histiocytosis at increased incidences in the dosed female rats and various lesions of the liver at increased incidences in the dosed male mice. The NTP concluded that under the conditions of this bioassay, BHT was not carcinogenic for F344 rats or B6C3F1 mice.

In a study conducted by Shirai et al., (1982) groups of approximately 50 male and 50 female B6C3F1 mice were given butylated hydroxytoluene (BHT) at concentrations of 200, 1000 or 5000 ppm in their diet for 96 wk followed by a

basal diet for 8 wk and were then killed. Similar groups of male and female controls were given basal diet throughout the 104 wk. Females given 1000 or 5000 ppm BHT and males given 500 0 ppm showed reduced weight gain. Neither survival rates nor food consumption differed between experimental and control groups. No significant changes attributable to BHT treatment were found in the haematological examinations or serum and urine analyses. Tumours were found in many organs; especially the lungs, liver, lymph nodes and spleen, in both the experimental and control groups, but none were related to BHT treatment. Thus the authors conclude this experiment provided no evidence of BHT carcinogenicity in mice.

In the present study Altmann et al., (1985) aimed to establish whether substances with a similar chemical structure to BHA induce d forestomach lesions. BHA was compared with some related chemicals in 28 day feeding studies. For this purpose gr oups of 5 to 10 Wistar rats were fed diets containing 2% BHA, 2% tert.-butylhydroquinone (TBHQ), 2% 4-methoxyphenol, 2% 1,4-dimethoxybenzene, 2% hydroquinone or 1% butylated hydroxytoluene (BHT), respectively, for periods of 4 weeks. BHA treatment caused s evere diffuse hyperplasia, acanthosis and hyperkeratosis in the forestomach mucosa which was most pronounced in the vicinity of the limiting ridge. In TBHQ treated animals brownish discolorations of the mucosa and mild hyperplasia with focally increased hy perplasia of basal cells were observed. In the case of p-hydroxyanisole a circular deep ulceration parallel to the limiting ridge occurred with hyperplasia and mild hyperkeratosis in the adjoining mucosa. Hydroquinone caused only mild hyperplastic and hyperkeratotic areas near the oesophageal entry in a few cases. The feeding of BHT induced no visible forestomach lesions. The strong effects of BHA and 4-methoxyphenol and the more or less inactivity of BHT and hydroquinone indicate that the methoxy group of the tested anisoles might be involved in their hyperplasiogenic activity.

Umemura *et al.,* (2009) report on a the validation of a 9-week in vivo rasH2/butylhydroxytoluene (BHT) model for the detectio n of genotoxic lung carcinogens, using six potent positiv e test compounds, dimethylnitrosamine (DMN; 15 mg/kg, i.p.), diethylnitrosamine (DEN; 100 mg/kg, i.p.), ethylnitrosourea (ENU; 120 mg/kg, i.p.), 3-methylcholanthrene (MC; 100 mg/kg, i.p.), 7,12-dimethylbenz(a)anthracene (DMBA; 5 mg/kg, i.g.) and benzo(a)pyrene (B(a)P; 80 mg/kg, i.p.), each given to rasH2 mice of both genders by single administration for initiation followed by promoter BHT treatment. Statistically significant increase in the incidence and multiplicity of lung tumors was observed in rasH2 mic e treated with BHT following exposure to all of the carcinogens tested. The authors concluded that the data suggests the rasH2/BHT model to be a powerful screening tool for genotoxic lung carcinogens.

Both carcinogenic and anticarcinogenic properties have been reported for the synthetic antioxidants butylated hydroxyanisole (BHA) and butylated hydroxytoluene (BHT). The association between dietary intake of BHA and BHT and stomach cancer risk was investigated by Botterweck et al., (2000) in the Netherlands Cohort Study (NLCS) that started in 1986 among 120,852

men and women aged 55 to 69 years. A semi-quantitative food frequency questionnaire was used to assess food consumption. Information on BHA or BHT content of cooking fats, oils, mayonnaise and other cr eamy salad dressings and dried soups was obtained by chemical analysis, a Dutch database of food additives (ALBA) and the Dutch Compendium of Foods and Diet Products. After 6.3 years of follow-up, complete data on BHA and BHT intake of 192 incident stomach cancer cases and 2035 subcohort members were available for case-cohort analysis. Mean intake of BHA or BHT among subcohort members was 105 and 351 microg/day, respectively. For consumption of mayonnaise and other creamy salad dressings with BHA or BHT no association with stomach cancer risk was observed. A statistically non-significant decrease in stomach cancer risk was observed with increasing BHA and BHT intake [rate ratio (RR) highest/lowest intake of BHA = 0.57 (95% confidence interval (CI): 0.25-1.30] and BHT = 0.74 (95% CI: 0.38-1.43). In this study, no significant association with stomach cancer risk was found for usual intake of low levels of BHA and BHT.

Inhalation toxicity

In order to investigate the possibility of developing a rapid *in vivo* as say for lung carcinogens, Umemura *et al* ., (2001) examined whether the tumo ur-promoting activity of butylhydroxytoluene (BHT) is efficacious in rasH2 mice. METHODS: rasH2 mice and wild littermates of both genders were pre-treated with carcinogens [urethane (UR), 4-nitroquinoline 1-oxide (4NQO) or diethylnitrosamine (DEN)], and, one day later, given a 400 mg/kg dose of BHT. Six weeks after the initiation treatment, evidence of carcinogenicity could be detected in male and female rasH2 mice that had received UR doses of > or = 250 mg/kg and > or = 125 mg/kg, respectively, prior to exposure to BHT, whereas only 500 mg/kg of UR was sufficient to induce tumo urs in female rasH2 mice given the carcinogen a lone. The carcinogenicity of 15 mg/kg of 4NQO could be detect ed after 9 weeks in male rasH2 mice given the carcinogen followed by BHT. Similarly, the carcinogenicity of 60 mg/kg of DEN could be detected after 9 weeks and 6 weeks, respectively, in male and female rasH2 mice given the carcinogen followed by BHT. No ca rcinogenicity could be demonstrated through the experimental period with doses of 4NQO or DEN given alone. These results indicate that BHT administration increases the susceptibility of rasH2 mice to lung carcinogens, and suggest that the use of BHT in ras H2 mice might lead to the establishment of a rapid in vivo assay for lung carcinogens.

Dermal Toxicity

It is reported by Taniguchi et al., (1996) that t umor necrosis factor-alpha (TNF-alpha) has been demonstrated to selectively decrease the production of type I and type III collagens in human dermal fibroblasts. The effects of the commonly used food antioxidants, butylated hydroxyanisole (BHA), butylated hydroxytoluene (BHT), alpha-tocopherol, propyl gallate, superoxide dismutase (SOD), and catalase on TN F-alpha-induced growth enhancement and collagen metabolism were evaluated in the present study. BHA at concentrations of both 5 x 10(-5) and 10(-4) M inhibited cell proliferation and

DNA synthesis induced by 10 ng/ml TNF-alpha in human dermal fibroblasts, while other antioxidants had minimal effects. Further, BHA (5 x 10(-5) M and 10(-4) M) significantly blocked TNF-alpha-induced decreases in collagen synthesis. The authors conclude that the results suggest that antioxidants such as BHA may be involved in the modulation of collagen synthesis by TNF-alpha in human dermal fibroblasts.

Reproductive and developmental toxicity

In a study conducted by McFarlane et al., (1997) the livers of rats fed diets containing butylated hydroxytoluene (BHT) over two generations in two separate studies. BHT did not produce tumours when tested for carcinogenicity in several studies by the conventional way. However, when BHT was given to rats in a two-generation carcinogenicity study, a high incidence of hepatic tumours was found in males but not in female rats of the F1 generation. A sequential study has been carried out to gain an insight into this unexpected finding, paying particular attention to the perinatal period. In the dose-ranging study designed to assess the tolerance of rats to BHT, groups of male and female rats (F0 generation) were fed diets calculated to deliver 0, 500, 750 and 1000 mg/kg body weight/day. Following a loading period of 5 wk the rats were mated. The BHT content of the diet was not adjusted during pregnancy and lactation. Owing to the normal increase in food consumption during lactation, intakes peaked at double the nominal value by 21 days after the birth of pups. At this time the pups (F1) were weaned onto control diet and maintained on it for 4 wk. At birth, the body weights of pups from the BHT-treated dams were comparable to those of the controls but at weaning the body weights of the pups from all three dose levels were less than those of the controls. At the termination of the experiment (4 wk after weaning), the pups from BHT-treated dams still weighed less than those from untreated controls. In the main experiment the F0 generation were fed 0, 25, 100 and 500 mg/kg body weight/day. Their offspring (F1 generation) were weaned on diets containing the same amount of BHT as the respective parents, apart from the group given the highest dose level (500 mg/kg body weight/day). This dose level was reduced to 250 mg/kg body weight/day at weaning in order to conform with previously published findings. The pups from the dams given the highest dose level were maintained on a dietary concentration of 250 mg/kg body weight/day for the entire study. A group of age-matched non-pregnant females was also studied and the results obtained compared with those from pregnant dams. Pups from all groups were examined at day 20 of gestation, at weaning (21 days after birth), and at 4 and 22 wk post-weaning. There were no effects on fertility and no increase in foetal abnormalities at any dose of BHT. Dams receiving BHT at a nominal dose of 500 mg/kg body weight/day showed liver enlargement accompained by induction of pentoxyresorufin O-dependentylase and glutathione S-transferase, and proliferation of the endoplasmic reticulum. Pups from these dams were of the same weight at birth as controls but lost weight during the lactation period. This deficit was not recovered by the time the experiment was terminated. Hence, in two independent studies, the only significant finding in rats treated with BHT *in utero* and during lactation was that the weight gain of pups during lactation was less than expected when dams received at least 500 mg BHT/kg

body weight/day. The body weight of pups did not return to normal following a return to a control diet for 4 wk. It is postulated that the re tardation in weight gain of the pups could be due to inadequate milk production.

In a study conducted by Olsen et al., (1986) g roups of 60, 40, 40 and 60 F0 Wistar rats of each sex were fed a semi-synthetic diet containing butylated hydroxytoluene (BHT) i n concentrations to provi de intakes of 0, 25, 100 or 500 mg/kg body weight/day, respectively. The F0 rats were mated and groups of 100, 80, 80 or 100 F1 rats of each sex wer e formed from 40, 29, 30 and 44 litters, respectively. After weaning, the highest d ose (500 mg BHT/kg/day) was lowered to 250 mg/kg/day for the F1 rats. The numbers of litters of ten or more pups at birth decreased with increasing BHT dose. At weaning, treated F1 rats had lower body weights than the controls, the extent of the reduction being dose related; the effect, which persisted throughout the study, was most pronounced in the males. The survival of BHT-treated F1 rats of both sexes was significantly better than that of the controls. No significant changes attributable to BHT treatme nt were found in the haematological parameters. F1 females on the highest dose showed an increase in serum cholesterol and phospholipids, and serum triglycerides were reduced in this group in both sexes. Dose-related increases in the numbers of hepatocellu lar adenomas and carcinomas were statistically significant (at P less than 0.05 or lower) in male F1 rats when all groups together were tested for heterogeneity or analysis for trend. The increase in hepatocellular adenomas and carcinomas in treated female F1 rats was only statistically significant for adenomas (at P less than 0.05) in the analysis for trend. All hepatocellular tumours were detected when the F1 rats were more than 2 yr old. Tumours were found in many other organs of some of the treated rats , but their incidence was not significantly different from that in controls. The role of BHT in the development of hepatocellular tumours requires further elucidation.

Other relevant studies

The widespread use of antioxidants in the food processing indus tries, especially oil and oil based ones, has great economic advantages. Yet since the ban on the further usage of butylated hydroxyanisole (BHA) and butylated hydroxytoluene (BHT) by the FAO in 1980, there have been several reports indicating that BHA and BHT might have both beneficial and detrimental effects. Studies were performed by Jayalakshmi and Sharma (1986) in healthy mature rats both males and females in a 1:1 ratio. In vitro estimations of the percentage h aemolysis (50% h aemolysis indicating a 50 % toxicity level) showed that BHT is more toxic than BHA and the h aemolytic activities (kinetics) showed a peak at 60-65% after 12 min with BHT and at 50% after 20 min with BHA. This clearly indicates that at the concentrations of 0.75%, BHA and BHT are harmful to the blood. Further work of dietary effects on blood is in progress. Thus while BHA and BHT are known to be metabolized in the liver and eliminated through the urine, they might be very detrimental to the circulatory system.

In the present study S uh *et al.,* (2005) aimed to establish the estimated daily intake (EDI) of antioxidants such as butylated hydroxyanisole (BHA), butylated

hydroxytoluene (BHT) and tert-butyl hydroquinone (TBHQ) in Korea. The EDIs were obtained from two sources. One of the es timations was based on the analytical determination of BHA, BHT and TBHQ in 12 food categories (ten food categories for TBHQ) and on individual dietary intake data obtained from the National Health and Nutrition Survey in 1998 (n=11 525, age > 1 year). The other EDIs of BHA, BHT and TBHQ were based on the maximum permitted levels specified in national food standards in Korea and on individual dietary intake data obtained from the National Health and Nutrition Survey in 1998 (n = 11 525, age > 1 year). To establish the EDIs based on the analytical determination and on individual dietary intake data, 133 food samples in 12 food categories were selected from the foods considered to be representative sources of BHA, BHT and TBHQ in the Korean diet. Selected samp les were analysed by GC with FID. BHA was not detected in any of the samples analysed. BHT and TBHQ were detected in the samples, but the levels were significantly lower than their maximum limits. The EDIs1 of BHT, and TBHQ for average consumers were 0.015 6(-3), and 0.0012(-3) mg kg(-1) body weight bw day(-1) and as a proportion of the ADI were 0.0052 and 0.0002%, respectively. For 95th percentile consumers, the EDIs of BHT and TBHQ were 0.0080 and 0.0006 mg kg(-1) bw day(-1), and as a proportion of the ADI were 2.67 and 0.09%, respectively. EDIs for BHA, BHT and TBHQ based on the maximum permitted levels and on individual dietary intake data were 0.04, 0.04 and 0.04 mg kg(-1) bw day(-1), respectively. The EDIs of BHA, BHT and TBHQ for average consumers rang ed from 6.00 to 14.42% of the ADI of each antioxidant. According to these results, the EDIs of BHA, BHT and TBHQ in Korea were significantly lower than ADI of these antioxidants established by the JECFA.

Behavioural data:

No data identified

***In vitro* Toxicity Status**

Carcinogenicity and mutagenicity

In a study conducted by Hageman et al., (1988), t he phenolic antioxidants butylated hydroxyanisole (BHA), butylated hydroxytoluene (BHT) and tert.-butylhydroquinone (TBHQ) were reassessed for mutagenic activi ty using the Salmonella tester strains TA97, TA102 and TA104, and in addition TA100. None of the phenolic antioxidants showed mutagenic activity, either with or without metabolic activation. At doses of 100 micrograms/plate and higher all 3 phenolic antioxidants exhibited toxic effects. A modification of the assay using the preincubation procedure with strain TA104 did not affect mutation frequencies. Combinations of BHA and BHT, tested to detect possible synergistic effects, did not exert mutagenic activity.

The mutagenicity of the smoke condensate was assayed in the *Salmonella* plate incorporation [Ames] assay with the tester strain TA98 in the presence of an S9 metabolic activation system. The cytotoxicity of the cigarette condensate was determined in the neutral red uptake assay and the (3-(4,5-

dimethylthiazol-2-yl)-5-(3-carboxymethoxyphenyl)-2-(4-sulfophenyl)-2H tetrazolium, inner salt assay (MTS assay) with the human hepatocellular liver carcinoma cell line, HEP-G2. It was concluded that the *in vitro* mutagenicity and cytotoxicity of the cigarette smoke was not increased by the addition of the ingredients, which included *butylated hydroxytoluene* at levels up to 1 ppm.

In vitro toxicity testing of tobacco ingredients in burnt form (Internal document R-25).

In a study conducted by Redente *et al*., (2010) two chronic lung inflammation models (repeated exposure to butylated hydroxytoluene (BHT) and infection with Mycobacterium tuberculosis) were used to establish whether similar macrophage phenotype changes occur in non-neoplastic pulmonary disease. In both models, pulmonary IFN-gamma and IL-4 production coincided with altered polarization of alveolar macrophages. As inflammation progressed in both models, the amount of BALF IFN-gamma content and BAL macrophage iNOS expression decreased, and BALF IL-4 content and macrophage arginase I expression rose, indicating alternative/M2 polarization. BDMCs from BHT-treated mice displayed polarization profiles similar to alveolar macrophages, but BDMCs in M. tuberculosis-infected mice did not become polarized. Thus the authors conclude that only alveolar macrophages in these two models of chronic lung disease exhibit a similar progression of polarization changes; polarization of BDMCs was specific to BHT-induced pulmonary inflammation, and polarization of granuloma macrophages was specific to the M. tuberculosis infection.

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