

Butylated Hydroxytoluene (2,6-Bis(1,1-dimethylethyl)-4-methylphenol)

Butylated hydroxytoluene (BHT) is used as an antioxidant/preservative in foods at levels ranging from 10 to 200 ppm. Current food regulations establish a maximum content of 0.02 percent for all antioxidants combined. Industrial applications of BHT include use as an antioxidant in rubber, petroleum, and plastic products.

Butylated hydroxytoluene passed the animal data screen, underwent a preliminary toxicological evaluation, and is being brought to the Carcinogen Identification Committee for consultation. This is a compilation of the relevant studies identified during the preliminary toxicological evaluation.

Epidemiological data

No cancer epidemiology studies were identified.

Animal carcinogenicity data

- Long-term diet studies
 - 107 to 108-week diet studies in male and female B6C3F₁ mice: NCI (1979)
 - *Increase in alveolar/bronchiolar carcinomas or adenomas (by pairwise comparison) in females*
 - *No treatment-related tumor findings in males*
 - 105-week diet studies in male and female Fischer 344 rats: NCI (1979)
 - *No treatment-related tumor findings in males or females*
 - 104-week diet studies in male and female Wistar rats: Hirose (1981)
 - *No treatment-related tumor findings in males or females*
 - 10-month diet studies in male and female C3H mice: Lindenschmidt (1986, p. 155)
 - *Increase in liver tumors (by pairwise comparison) in males*
 - *No treatment-related tumor findings in females*
- Two-generation diet studies in rats
 - Male and female Wistar rats dosed for entire lifespan: Olsen (1986, p 5)
 - *Increase in hepatocellular adenoma, carcinoma, or adenoma and carcinoma combined (by pairwise comparison and trend) in males*
 - *Increase in hepatocellular adenomas (by pairwise comparison) in females*

Other relevant data

- Genotoxicity: as reviewed in Bombard *et al.* (2002)
 - Mutagenicity tests with tester strains *Salmonella typhimurium* TA92, TA94, TA97, TA98, TA102, TA104, TA100, TA1530, TA1535, TA1537, TA1538, G46, *E. coli* (*negative*)
 - Sex-linked recessive lethal mutations in *Drosophila melanogaster* (*negative*)
 - Silk worm specific locus mutagenicity test (*negative*)
 - Mammalian point mutations HGPRT locus (*negative*)
 - Mouse lymphoma assay (*positive*)
 - *In vivo* specific locus test in mice (*negative*)
 - Chromosome abnormalities in onion (*positive and negative*), and barley and crepis (*negative*)
 - In *Drosophila melanogaster*, chromosome loss (*positive*), dominant lethal (*negative*), and reciprocal translocation (*negative*)
 - *In vitro* clastogenic and chromosomal aberrations in mammalian cells – human embryonic lung cells (*positive for anaphase chromosomes*), CHO (*positive*), Chinese hamster lung (*negative*)
 - *In vivo* clastogenic effects and chromosome aberrations, in rat bone marrow (*negative*), mouse micronuclei (*negative*), mouse germ cell (*positive and negative*), rat germ cell (*negative*)
 - DNA interactions, rec-assay (*positive and negative*), SOS-chromotest (*negative*), *in vitro* sister chromatid exchange in hamster lung, ovarian and DON cells (*negative*)
- Structure activity considerations
 - Structurally similar to butylated hydroxyanisole, a listed Proposition 65 carcinogen and IARC Group 2B carcinogen
- Modifies carcinogenicity
 - Tumor promoting activities in mouse lung: Thompson *et al.* (1989)
 - Tumor promoting activities in DBN-initiated esophageal carcinogenesis: Fukushima (1983) as reviewed in Hirose (1993).
 - Tumor promoting activities in DBN, BBN, MNU-initiated urinary bladder carcinogenesis: Imaida (1983) as reviewed in Hirose *et al.* (1993)
 - Tumor promoting activities in DMH-initiated colon tumors in BALB/c mice (Lindenschmidt *et al.*, 1986)
 - Inhibits kidney and colon carcinogenesis in DMH-initiated rat colon carcinogenesis: Shirai (1985) as reviewed in Hirose *et al.* (1993).

Reviews

- IARC (1986)
- IARC (1987)

References¹

- Bomhard EM, Bremmer JN, Herbold BA (2002). Review of the mutagenicity/genotoxicity of butylated hydroxytoluene. *Mutat Res* **277**:187-200.
- Hageman GJ, Verhagen H, Kleinjans, JCS (1988). Butylated hydroxyanisole, butylated hydroxytoluene and tert-butylhydroquinone are not mutagenic in the Salmonella/microsome assay using new tester strains. *Mutat Res* **208** (3-4):207-211.
- Hirose M, Shibata M, Hagiwara A, Imaida K, Ito N (1981). Chronic toxicity of butylated hydroxytoluene in Wistar rats. *Cosmet Toxicol* **19**:147-151.
- International Agency for Research on Cancer (1986). IARC Monographs on the Evaluation of Carcinogenic Risks to Humans. *Some Naturally Occurring and Synthetic Food Components, Furocoumarins and Ultraviolet Radiation*. Volume 40. pp. 161-206. IARC, Lyon, France.
- International Agency for Research on Cancer (1987). IARC Monographs on the Evaluation of Carcinogenic Risks to Humans. *Overall evaluations of carcinogenicity: An updating of IARC's monographs volume 1-42*. Suppl 7, p. 59, IARC, Lyon, France.
- Lindenschmidt RC, Tryka AF, Goad ME, Witschi HP (1986). The effects of dietary butylated hydroxytoluene on liver and colon tumor development in mice. *Toxicol* **38**:151-160.
- National Cancer Institute (1979). Bioassay of butylated hydroxytoluene for possible carcinogenicity. U.S. Department of Health, Education, and Welfare, Public Health Service, National Institute of Health. National Cancer Institute, DHEW Publication No. (NIH) 79-1706.
- Olsen P, Meyer O, Bille N, Würzen G (1986). Carcinogenicity study on butylated hydroxytoluene (BHT) in Wistar rats exposed *in utero*. *Food Chem Tox* **24** (91):1-12.
- Thompson JA, Schullek KM, Fernandez CA, Malkinson AL (1989). A metabolite of butylated hydroxytoluene with potent tumor-promoting activity in mouse lung. *Carcinogenesis* **10**: 773-775.
- Yoshida Y (1990). Study on mutagenicity and antimutagenicity of BHT and its derivatives in a bacterial assay. *Mutat Res* **242** (3):209-217.

¹ Excerpts or the complete publication have been provided to members of the Carcinogen Identification Committee, in the order in which they are discussed in this document.