UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

OFFICE OF PREVENTION,
PESTICIDES, AND TOXIC SUBSTANCES

DATE: September 29, 2005

ACTION MEMORANDUM

SUBJECT: Inert Ingredient Reassessment - Butylated Hydroxyanisole (25013-16-5)
Butylated Hydroxytoluene (128-37-0)

FROM: Pauline Wagner, Chief Pauline Wagner 9/29/05
Inert Ingredient Assessment Branch
Registration Division (7505C)

TO: Lois A. Rossi, Director Donald R Stubbs
Registration Division (7505C)

I. FQPA REASSESSMENT ACTION

Action: Reassessment of four inert ingredient exemptions from the requirement of a tolerance. The exemptions are being reassessed as-is.

Chemicals:

CFR Citation				CAS Reg. No. Name
40 CFR §	Inert Ingredients	Limits	Uses	
180.910*	Butylated hydroxyanisole	(none)	Antioxidant	25013-16-5 phenol, (1,1-dimethylethyl)-4-methoxy-
180.930**	Butylated hydroxyanisole	(none)	Antioxidant	25013-16-5 phenol, (1,1-dimethylethyl)-4-methoxy-
180.910*	Butylated hydroxytoluene	(none)	Antioxidant	128-37-0 phenol, 2,6-bis(1,1-dimethylethyl)-4-methyl-
180.930**	Butylated hydroxytoluene	(none)	Antioxidant	128-37-0 phenol, 2,6-bis(1,1-dimethylethyl)-4-methyl-

Use Summary: BHA and BHT are used as antioxidants in pesticide formulations, with typical concentrations in food-use pesticide products <0.2%. They are also used as direct additives in food and in a wide variety of personal care, pharmaceutical, and industrial products.

List Reclassification Determination: The current List Classification for BHA and BHT is 3. Because EPA has determined that there is a reasonable certainty that no harm to any population subgroup will result from aggregate exposure to BHA and BHT when used as antioxidants in pesticide formulations, the List Classification for BHA and BHT will change from List 3 to List 4B.

II. MANAGEMENT CONCURRENCE

I concur with the reassessment of the four exemptions from the requirement of a tolerance for the inert ingredients butylated hydroxyanisole (BHA) (CAS Reg. No. 25013-16-5) and butylated hydroxytoluene (BHT) (CAS Reg. No. 128-37-0) and with the List reclassification determination, as described above. I consider the four exemptions established in 40 CFR part 180.910 and 180.930 to be reassessed for purposes of FFDCA's section 408(q) as of the date of my signature, below. A Federal Register Notice regarding this tolerance exemption reassessment decision will be published in the near future.

Donald n Stubbs

Lois A. Rossi, Director
Registration Division

9/30/05

Date:

cc: Debbie Edwards, SRRD
Joe Nevola, SRRD

UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
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OFFICE OF PREVENTION, PESTICIDES, AND TOXIC SUBSTANCES

September 29, 2005

MEMORANDUM

SUBJECT: Reassessment of the Four Exemptions from the Requirement of a Tolerance for Butylated Hydroxyanisole (BHA) and Butylated Hydroxytoluene (BHT)

FROM: Keri Grinstead
Inert Ingredient Assessment Branch (IIAB)
Registration Division (7505C)

TO: Pauline Wagner, Chief
Inert Ingredient Assessment Branch (IIAB)
Registration Division (7505C)

Background

Attached is the science assessment for butylated hydroxyanisole (BHA) and butylated hydroxytoluene (BHT). Both chemicals have an exemption from the requirement of a tolerance under 40 CFR 180.910 and 40 CFR 180.930, as listed in Table 1. This assessment summarizes available information on the use, physical/chemical properties, toxicological effects, exposure profile, environmental fate, and ecotoxicity of BHA and BHT. The purpose of this document is to reassess the four existing exemptions from the requirement of a tolerance for residues of BHA and BHT when used as inert ingredients in pesticide formulations as required under the Food Quality Protection Act (FQPA).

Executive Summary

This report evaluates two chemicals, butylated hydroxyanisole (BHA) (CAS Reg. No. 25013-16-5) and butylated hydroxytoluene (BHT) (CAS Reg. No. 128-37-0). Both BHA and BHT have exemptions from the requirement of a tolerance when used as inert ingredients in pesticide formulations under 40 CFR 180.910 when applied to growing crops or raw agricultural commodities after harvest and under 40 CFR 180.930 when applied to animals.

BHA and BHT are used as antioxidants in pesticide formulations, with typical concentrations in food-use pesticide products <0.2%. They are also used in a wide variety of food, personal care, pharmaceutical, and industrial products. Both chemicals

are classified as Generally Recognized as Safe (GRAS) by the Food and Drug Administration (FDA) as additives added directly to food with a limitation as antioxidants, of not over a total of 0.02 percent of the fat and oil content of food. The 21 CFR citations for their use in food products are listed in Appendix A and their FDA-approved uses as inactive ingredients in drug products are listed in Appendix B.

Extensive information is available to address the toxicity of BHA and BHT. BHA and BHT are of low acute oral and dermal toxicity, slightly irritating to the skin and eyes of animals, and not considered to be dermal sensitizers. The level of BHA causing no toxicological effect from repeat-dose oral administration in the rat is considered to be 50.0 mg/kg bw/day (0.1 % in the diet). Long-term oral studies of BHT resulted in a NOAEL of 25 mg/kg bw/day, with decreased body weight gain at the next higher dose of 225 mg/kg bw/day. Overall, BHA and BHT are not considered mutagenic. BHA was not a dermal carcinogen and chronic feeding only produced tumors specific to the forestomach of rodents. For the possible carcinogenic and tumor-promoting effect of repeat oral dosages of BHT, a threshold level of 100 mg/kg bw/day was assumed based on no increase in liver carcinoma but slight increase in liver adenoma seen at the 100 mg/kg bw/day dosage (NOEL of 25 mg/kg bw/day). Reproductive and developmental effects of BHA and BHT were only at dose levels >220 mg/kg/day, far exceeding any dose likely to be received as a result of their use as antioxidants in pesticide products.

Both chemicals are absorbed in the gastrointestinal tract and metabolized and excreted by the body. BHT also demonstrates some slight dermal absorption.

As inert ingredients in pesticide formulations, EPA expects that exposure to BHA and BHT would primarily be via the oral route, through consumption of agricultural crops to which these chemical have been applied. Typical concentrations of BHA and BHT in food-use pesticide products are <0.2%. Additional inhalation, dermal, and oral exposure may occur from residential use of pesticide products containing these inert ingredients.

Taking into consideration all available information on BHA and BHT, including their long history of use as direct food additives and their use in cosmetics, pharmaceuticals, and personal care products, it has been determined that there is a reasonable certainty that no harm to any population subgroup will result from aggregate exposure to BHA or BHT when used as inert ingredients in pesticide formulations when considering dietary exposure and all other non-occupational sources of pesticide exposure for which there is reliable information. Therefore, it is recommended that the four exemptions from the requirement of a tolerance established for residues of BHA and BHT, as listed in Table 1, can be considered reassessed as safe under section 408(q) of the FFDCA.

I. Introduction

This report provides a qualitative assessment for BHA and BHT, pesticide inert ingredients used as antioxidants in pesticide formulations. Both chemicals have exemptions from the requirement of a tolerance under 40 CFR 180.910 and 180.930.

II. Use Information

A. Pesticide Uses

BHA and BHT are used as antioxidants in pesticide formulations. Antioxidants react quickly with free radicals, terminating chain reactions and slowing oxidation of substrates. This process ultimately slows oxidation of industrial materials during prolonged storage and substantially increases food shelf life by delaying the deterioration of food odors and flavors. The exemptions from the requirement of a tolerance for BHA and BHT when used as inert ingredients in pesticide formulations are provided in Table 1 below.

Table 1. Pesticide Uses

CFR Citation				CAS Reg. No. /Name
40 CFR §	Inert Ingredients	Limits	Uses	
180.910*	Butylated hydroxyanisole	(none)	Antioxidant	25013-16-5 phenol, (1,1-dimethylethyl)-4-methoxy-
180.930**	Butylated hydroxyanisole	(none)	Antioxidant	25013-16-5 phenol, (1,1-dimethylethyl)-4-methoxy-
180.910*	Butylated hydroxytoluene	(none)	Antioxidant	128-37-0 phenol, 2,6-bis(1,1-dimethylethyl)-4-methyl-
180.930**	Butylated hydroxytoluene	(none)	Antioxidant	128-37-0 phenol, 2,6-bis(1,1-dimethylethyl)-4-methyl-

*Residues listed in 40 CFR 180.910 are exempt from the requirement of a tolerance when used in accordance with good agricultural practice as inert (or occasionally active) ingredients in pesticide formulations applied to growing crops or to raw agricultural commodities after harvest.

**Residues listed in 40 CFR 180.930 are exempt from the requirement of a tolerance when used in accordance with good agricultural practice as inert (or occasionally active) ingredients in pesticide formulations applied to animals.

B. Other Uses

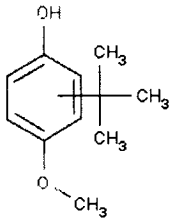
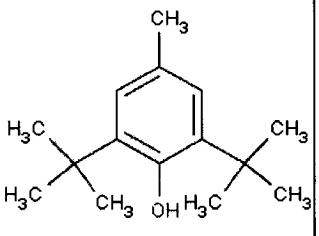
BHA and BHT are used in a wide variety of food, personal care, pharmaceutical, and industrial products. The 21 CFR citations for their use in food products are listed in Appendix A. Their use as inactive ingredients in approved drug products are listed in

Appendix B. BHA and BHT are used in petroleum products, waxes, synthetic and natural rubbers, paints, inks, plastics, and elastomers to protect these materials from oxidation during prolonged storage. They are also used in food products and animal feeds to retard rancidification and other oxidative reactions of animal fats, vegetable oils, and oil soluble vitamins. Both chemicals are also used in cosmetics, soaps, and food packaging materials such as waxed paper, paperboard, and polyethylene.

III. Physical and Chemical Properties

BHA is a white or slightly yellow waxy solid with a faint characteristic odor. BHA is a mixture of 3-tert-butyl-4-hydroxyanisole and 2-tert-butyl-4-hydroxyanisole. BHT (2,6-di-tert-butyl-p-cresol) is a white, crystalline solid with a slight phenolic odor. Both BHA and BHT are prepared synthetically and are not known to occur naturally. The chemical structures and some of the physical and chemical properties of BHA and BHT are listed in Table 2 below.

Table 2. Physical and Chemical Properties

	BHA (CAS Reg. No. 25013-16-5)		BHT (CAS Reg. No. 128-37-0)	
Parameter	Value	Source	Value	Source
Structure		ChemID[1]		ChemID
Molecular formula	$C_{11}H_{16}O_2$	ChemID	$C_{15}H_{24}O$	SRC[2]
Physical Form	White or slightly yellow, waxy solid		Colorless solid at room temperature	
Molecular Wt.	180.25		220.354	SRC
Melting Point	51° C Experimental	ChemID	71° C Experimental	ChemID
Water solubility	213 mg/L (25° C) Estimated	ChemID	0.6 mg/L (25° C) Experimental	ChemID
Vapor Pressure	2.48E-03 mm Hg (25° C) Estimated	ChemID	.00516 mm Hg (25° C)	SRC
Henry's Law Constant	1.17E-06 atm-m^3/mole(25° C) Estimated	ChemID	4.12E-06 atm-m^3/mole (25° C) Estimated	ChemID

	BHA (CAS Reg. No. 25013-16-5)		BHT (CAS Reg. No. 128-37-0)	
Parameter	Value	Source	Value	Source
Octanol-water partition coefficient K_{ow}	3.500 Estimated	ChemID	5.1 Experimental	ChemID

[1]ChemIDplus Advanced on TOXNET (http://www.toxnet.nlm.nih.gov/index.html)
[2]SRC – Syracuse Research Corporation, Interactive PhysProp Database Demo, http://www.syrres.com/esc/physdemo.htm, 9/20/2005.

IV. Hazard Assessment

A. Hazard Profile

Extensive information is available defining the toxicity of BHA and BHT. Both chemicals are classified as Generally Recognized as Safe (GRAS) by the Food and Drug Administration (FDA) for direct and indirect human consumption and approved by the FDA as direct and indirect food additives with a tolerance for antioxidants, including BHA and BHT, of not over a total of 0.02 percent of the fat and oil content of food. Both BHA and BHT are "within the scope" of EPA's High Production Volume (HPV) Challenge Program[1]. BHA is currently "not sponsored" under the HPV Program; however, BHT has full sponsorship by the International Council of Chemical Associations (ICCA) under the Organization for Economic Cooperation and Development (OECD).

This hazard assessment was developed using the 2002 OECD-SIDS[2] (Screening Information Data Set) Screening Initial Assessment Report (SIAR) and Profile (SIAP) for 2,6-di-tert-butyl-p-cresol (BHT), the International Agency for Research on Cancer (IARC)[3] website, a 1986 IARC review of BHA, and numerous peer-reviewed studies and evaluations.

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[1]The goal of the HPV program is to collect and make publicly available a complete set of baseline health and environmental effects data on those chemicals that are manufactured in, or imported into, the United States in amounts equal to or exceeding one million pounds per year. Industry sponsors volunteer to evaluate the adequacy of existing data and to conduct tests where needed to fill the gaps in the data, and EPA (and the public) has an opportunity to review and comment on the sponsors' robust summary report.

[2]The Screening Information Data Set (SIDS) Program which is under the auspices of the Organizations for Economic Cooperation and Development (OECD), is a voluntary cooperative international testing program that began in 1989. It is focused on developing base level test information on approximately 600 poorly characterized international HPV chemicals. The SIDS data are used to "screen" the chemicals and set priorities for further testing or risk assessment/management activities. The priorities are set at the SIDS meeting (SIAM).

[3]In 1969, the International Agency for Research on Cancer (IARC) initiated a program to evaluate the carcinogenic risk of chemicals to humans and to produce monographs on individual chemicals. Each volume serves as an authoritative, independent assessment by international experts of the carcinogenic risk

B. Metabolism and Pharmacokinetics

BHA

Animal studies have established that BHA is absorbed from the gastrointestinal tract, metabolized to the BHA glucuronide and ethereal sulfate, and excreted in the urine and feces.

Rats were administered a single oral dose of 0.4 g BHA/kg with urinary excretion of the BHA glucuronide and ethereal sulfate during the 5 days after dosing accounting for 61-82 and 11-16 percent of the dose, respectively. Five percent of the dose was excreted unchanged.

In a study with male rats, 87-96% of the administered BHA was eliminated via urine, feces, or respiration within 48 hours of ingestion. In a second study of rats administered methoxy labeled 3-BHA by gavage, 41% was found in the urine and 53% was found in the feces after 48 hours (IPCS 1989).

BHT (OECD SIDS 2002)

BHT is readily absorbed through the gastrointestinal tract and slightly through intact skin. It is then metabolized (several metabolic pathways and metabolites have been identified) and excreted primarily in the urine and, to a lesser degree, in the feces. In long-term feeding of diets containing BHT, the compound accumulated especially in adipose tissue with lower levels found in the liver. The elimination half-lives ranged from 7-10 days for both organs on cessation of treatment. An enterohepatic circulation takes place in rats, particularly for the metabolite BHT acid and its glucuronide. In rats, 80-90% of a single oral dose was found in the urine within four days, most within 24 hours. Rabbits excreted approximately 54% within four days.

C. Toxicological Data

BHA

Oral

Acute – Oral LD_{50} values for BHA ranged from 2.0 to > 5.0 g/kg in rats and 1.1 to 2.0 g/kg in mice.

Subchronic/Chronic – In a study of rats exposed to 0, 0.125, 0.25, 0.5, 1.0, or 2.0 % of BHA in the diet for 104 weeks, body weight gains were depressed in rats receiving at least 0.5% BHA; however, no significant pathology was seen in any site other than the forestomach epithelium, with significant damage only seen

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posed by a selected chemical, group of chemicals, industrial process, occupational exposure, lifestyle factor, or biological agent.

in animals exposed to > 0.5% BHA. The effects seen in the forestomach of rats and mice in repeat-dose studies are discussed in the carcinogenicity section below. In establishing the ADI for BHA, JECFA has evaluated the numerous repeat-dose studies on animals and determined the level causing no toxicological effect in the rat to be 0.1% in the diet, equivalent to 50.0 mg/kg bw/day.

Dermal (CIR 1984)

Acute - Acute dermal testing on rabbits of an eye makeup preparation containing 0.1% BHA yielded an LD_{50} > 2 g/kg.

Skin Irritation – Skin irritation testing of cosmetic products containing 0.1-0.2% BHA on rabbits indicated the products were mild to moderate skin irritants. There were no available reports of skin testing using the neat form of BHA.

Results of two guinea pig immersion tests conducted with bubble bath products containing 0.1% BHA indicated mild and moderate skin irritation and no indication of systemic toxicity.

Eye Irritation (CIR 1984)

Eye irritation testing of cosmetic products containing 0.2% BHA on rabbits resulted in minimal or mild skin irritation. In a third study, an eye makeup product containing 0.1% BHA was placed into the eyes of rabbits in a single application. All treated eyes were negative for conjunctival redness and chemosis, keratitis, and iritis.

Mutagenicity (IARC 1986)

After evaluation of numerous studies, the 1986 IARC Working Group determined that BHA was not mutagenic to *Salmonella typhimurium*, *Drosophila melanogaster* or to Chinese hamster cells *in vitro* and did not cause chromosomal effects in *D. melanogaster* or in cultured Chinese hamster cells. In *in vivo* testing, BHA was negative using *S.* typhimurium.

Carcinogenicity

Groups of 50 male and 50 female mice received weekly topical applications of 0, 0.1, or 10.0 mg BHA in 0.2 mL acetone for life on shaved skin. Of the 13-21 mice per group examined histologically, no skin tumors were observed (IARC 1986).

According to the 1984 CIR report, "no carcinogenesis was demonstrated following dietary administration of BHA to either rats (up to 0.12 percent for 21 to 22 months, or up to 0.1 percent for 2 years) or dogs (up to 250 mg/kg/day for 15 months, or up to 0.3 percent for 1 year)."

BHA has been shown to produce hyperplasia, papillomas, and carcinomas of the rodent forestomach in numerous feeding studies. Numerous studies have been conducted to further evaluate these effects, including those conducted on animals without a forestomach. IARC conclusions were: "...BHA induced only squamous-cell tumours of the forestomach in three rodent species. At high concentrations, the mode of action by which BHA produces forestomach tumours may involve a net production of free radicals during the long transit time in the forestomach, resulting in cytotoxicity and subsequent hyperplasia. Upon chronic administration of BHA, this hyperplasia is sustained, which leads to a tumour-promoting effect specific to the forestomach" (IARC 1999).

Reproductive/Developmental

BHA administered by gavage to pregnant rabbits on gestation days 7-18 in doses of 50, 200, or 400 mg/kg bw/day did not induce any teratological effect. The fetuses were removed and examined on day 28. No treatment related effects were seen on the number of corpora lutea, implantations, fetuses dead or alive, gross malformations, skeletal and internal malformations, or weight of the fetuses. It was also noted that none of the dams showed any signs of adverse effects during the dosing period. The NOAEL for both maternal and developmental toxicity was 400 mg/kg/day (Hansen 1978).

BHA was administered to rats at 0.125, 0.25, or 0.50% (110, 220, or 420 mg/kg/day pre-breeding) in the diet of males and females at least 14 days before mating and 1-14 days during breeding. The diet was maintained for pregnant females during gestation and lactation. The offspring from each dose group were also maintained on the same test diet for the remainder of the experiment (up to 90 days for most animals). The NOAEL for maternal toxicity was 0.5% (420 mg/kg/day). For offspring toxicity, a NOAEL of 0.25% (220 mg/kg/day) in the diet of dams and offspring, and a LOAEL of 0.5% (420 mg/kg/day) BHA in the diet of dams and offspring, based on reduced weight of progeny during lactation (14 and 21 days of age) and increased periweaning mortality (13.5%) (Voorhees et al., as cited in ORNL 2005).

BHT

The following toxicological information for BHT is summarized from the 2002 OECD SIDS document.

Oral

Acute – In an acute toxicity test on rats, no effects were seen in rats administered up to 2390 mg/kg bw BHT as an aqueous dispersion in gum arabicum (10% w/v).

Subchronic/Chronic - The OECD SIDS document references and discusses several repeated-dose studies. The conclusions for repeated-dose toxicity are as follows: "Long-term exposure to BHT can result in functional and histological changes of lung, liver, kidneys, and thyroid. Higher sub-acute and sub-chronic doses of BHT can cause death of mice or rats, either due to severe lung damage or massive hemorrhages. In the case of chronic oral exposure, liver and thyroid are the main targets. Doses above 25 mg BHT/kg bw/day resulted in thyroid hyperactivity, enlargement of the liver, and induction of several liver enzymes." The hepatic effects and formation of preneoplastic foci are discussed in the carcinogenicity section of this document.

A 28-day oral study conducted by Powell et al. (1986) with rats was considered by the OECD SIDS 2002 document as the critical study for deriving a NOAEL because, it focused primarily on hepatotoxic effects which seem to play a causative role in the development of BHT-related liver tumors. Rats were dosed by gavage at doses of 0, 25, 250, or 500 mg/kg bw/day for 7 and 28 days. The NOAEL was considered to be 25 mg/kg bw/day, with only slight evidence of cell damage, as indicated by glycogen accumulation seen at 250 mg/kg bw/day at both 7 and 28 days.

In a long-term feeding study of male rats fed diets containing 100, 300, 1000, 3000, or 6000 ppm BHT, the NOAEL was determined to be 1000 ppm (ca. 75 mg/kg bw/day) due to reduced body weight gain in the two highest dosed groups, and increased liver weight with the 6000 ppm dose.

Dermal

An LD_{50} of >2000 mg/kg bw was reported in a study of rats administered a single dermal dose of BHT as an aqueous dispersion in gum arabicum (10% w/v). BHT was slightly irritating to the intact and abraded skin of rabbits after a 24-hour semi-occlusive application. While the OECD SIDS document stated that there were no available relevant experimental data, it did state that there was no indication of a sensitizing potential in limited guinea pig studies.

Eye Irritation

In Draize testing on rabbits, BHT was slightly irritating to the eye and symptoms were completely reversible after 72 hours.

Mutagenicity

In both bacterial and mammalian test systems, BHT showed no potential to cause point mutations. It also demonstrated no overt clastogenic activity *in vitro* and no clastogenic activity *in vivo*.

Carcinogenicity

Discussion and summary of the information from the OECD SIDS document regarding carcinogenicity of BHT is reproduced below:

> "In several reviews (e.g. IARC 1986, WHO 1996), limited evidence for carcinogenicity of BHT for experimental animals was found and this was based on several oral studies with mice and rats. Either no differences in tumour incidences among exposed and control animals were found or inconsistent, i.e. increased incidences at low, but not at high doses, were noted. Of the more recent studies, two reports indicate an increased rate of hepatocellular tumours in mice (Inai et al. 1988) and rats (Olsen et al. 1986). Prompted by these results, three others studies (Price 1994; two by Williams et al. 1990a) were conducted with rats, which however could not verify these results."

> "BHT is not a genotoxic carcinogen. Carcinogenic effects observed in one long-term study with rats probably were caused by the specific study conditions which resulted in persistent induction of liver enzymes and/or deficiency of choline. However, it cannot be completely ruled out that the hepatotoxic effects caused by high and chronic doses of BHT may result in persistent cell proliferation, which is known as a possible mechanism of non-genotoxic carcinogens. In addition, depending on the application regime, BHT may exert either anticarcinogenic or tumour-promoting activity at relatively high doses. For the possible carcinogenic and tumour-promoting effect of BHT, a threshold level of 100 mg/kg bw/day can be assumed based on the results from the study of Olsen et al. with chronic BHT exposure starting in utero as a worst case scenario (no increase in liver carcinoma but slight increase in liver adenoma at 100 mg/kg bw/day; NOEL of this study at 25 mg/kg bw/day). From the carcinogenicity studies with rats and mice an overall NOAEL can not be directly derived."

Reproductive/Developmental Toxicity

Reproductive – In a three-generation study, mice received 0, 23, 68, 203, or 608 mg/kg bw/day BHT in the diet during premating, mating, gestation and lactation. There were no effects on the number litters, number of pups, litter size, litter weight and sex ratio in any dose group of F1 and F2 animals or on neurobehavioral parameters in F1 and F2 generations. Increased body weight of pups at the lowest dose was observed (OECD SIDS 2002).

There was no evidence of teratogenic effects in studies of rats and mice. During pregnancy, BHT had maternal effects on mice above oral doses of 240 mg/kg bw/day and the developmental NOEL was reported to be 800 mg/kg bw/day.

D. Special Consideration for Infants and Children

Studies with BHA indicated pup sensitivity only at doses of 220 mg/kg/day or greater. Developmental studies with BHT resulted in maternal effects at dose levels greater than 240 mg/kg bw/day with a developmental NOEL of 800 mg/kg bw/day. The dose levels where effects were seen are far greater than expected exposures from the antioxidant uses of BHA and BHT in pesticide products. Based on this information, there is no concern, at this time, for increased sensitivity to infants and children to BHA or BHT from their use as antioxidants in pesticide products. For these same reasons, a safety factor analysis has not been used to assess risk and, therefore, the additional tenfold safety factor for the protection of infants and children is also unnecessary.

V. Environmental Fate Characterization/Drinking Water Considerations

BHA

BHA has a short half-life in the atmosphere, with some photolysis likely. It does not undergo hydrolysis. Primary degradation will occur on the order of days to weeks with ultimate degradation (mineralization) in weeks to months.

BHT

BHT is relatively unstable under environmental conditions. It is indirectly photodegradable, decomposes in aqueous solution in natural sunlight with irradiation (ca. 75%) and without (ca. 40%), and is also not stable in soil with 63-82% of BHT decomposed in non-sterilized and 25-35% in sterilized soils within one day of incubation (OECD SIDS 2002).

Once these chemicals are applied to land in pesticide formulations, the partitioning to air will be low. While rapid decanting on the applied soil surfaces could result in volatilization, the ultimate sink for these chemicals is the soil/sediment compartment, with both biotic and abiotic processes driving degradation.

Based on all of the above information, the physical/chemical properties of BHA and BHT, and typical concentrations in food-use pesticide products of <0.2%, concentrations of these chemicals in drinking water (from runoff), are not expected from their use as antioxidants in pesticide products.

VI. Exposure Assessment

BHA and BHT are approved for use as antioxidants in pesticide formulations applied to growing crops and raw agricultural commodities after harvest and to animals. Their concentrations in food-use pesticide products typically are < 0.2% in formulation. They are also used as direct food additives, and in a wide variety of pharmaceutical, personal care, and industrial products. Both chemicals are classified as Generally

Recognized as Safe (GRAS) by the FDA for direct and indirect human consumption, with a tolerance for antioxidants, including BHA and BHT, of not over a total of 0.02 percent of the fat and oil content of food. The Joint FAO/WHO Expert Committee on Food Additives (JECFA) estimates of Acceptable Daily Intake (ADI) are 0-0.5 mg/kg bw for BHA and 0-0.3 mg/kg bw for BHT.

For the general population, the majority of exposure to BHA and BHT occurs from their use as direct food additives and from their use in pharmaceuticals and consumer products. The primary route of exposure from their use as inert ingredients in pesticide formulations is expected to be through consumption of food to which these chemicals have been applied. Based on their behavior in the environment, physical/chemical properties, and typical concentrations in food-use pesticide products of <0.2%, concentrations of BHA and BHT in drinking water (from runoff), are not expected from their use as antioxidants in pesticide products. Additional exposure may occur via the dermal and inhalation routes from residential use of pesticide products containing these inert ingredients.

VII. Aggregate Exposure

In examining aggregate exposure, FFDCA section 408 directs EPA to consider available information concerning exposures from the pesticide residue in food and all other non-occupational exposures, including drinking water from ground water or surface water and exposure through pesticide use in garden, lawns, or buildings (residential and other indoor uses).

For BHA and BHT, a qualitative assessment for all pathways of human exposure (food, drinking water, and residential) is appropriate given the lack of human health concerns associated with exposure to BHA and BHT when used as inert ingredients in pesticide formulations.

VIII. Cumulative Exposure

Section 408(b)(2)(D)(v) of the FFDCA requires that, when considering whether to establish, modify, or revoke a tolerance, the Agency consider "available information" concerning the cumulative effects of a particular pesticide's residues and "other substances that have a common mechanism of toxicity."

Unlike other pesticides for which EPA has followed a cumulative risk approach based on a common mechanism or toxicity, EPA has not made a common mechanism of toxicity safety finding as to BHA or BHT, and any other substances, and BHA and BHT do not appear to produce toxic metabolites produced by other substances. For the purpose of these tolerance actions, therefore, EPA has not assumed that BHA or BHT have a common mechanism of toxicity with other substances. For information regarding EPA's efforts to determine which chemicals have a common mechanism of toxicity and to evaluate the cumulative effects of such chemicals, see the policy statements released by EPA's Office of Pesticide Programs concerning common mechanism determinations

and procedures for cumulating effects from substances found to have a common mechanism on EPA's website at http://www.epa.gov/pesticides/cumulative/.

IX. Human Health Risk Characterization

For the general population, the majority of exposure to BHA and BHT would be from their extensive use in consumer and pharmaceutical products, and, particularly, as FDA-approved direct food additives. They are metabolized and excreted by the body, they have low acute toxicities, are only slightly irritating to the skin and eyes of rabbits, and are not dermal sensitizers. Effects from chronic oral exposures only occur at levels much greater than those expected from their use as antioxidants in pesticide products. For BHT, the critical study used by OECD SIDS resulted in an oral, repeat-dose NOAEL of 25 mg/kg bw/day; however, it is noted that the dosage where effects were seen was 250 mg/ kg bw/day, with no dosing between 25 and 250 mg/kg mw/day and a second study yielded a NOAEL of 75 mg/kg bw/day with reduced body weight gain at the next higher dose of 225 mg/kg bw/day. BHA and BHT are not mutagenic, BHT is not a genotoxic carcinogen, and carcinogenic effects observed with oral repeat dose studies of BHA on rodents were considered to be a non-systemic local effect specific to the rodent forestomach. Reproductive and developmental effects were only seen at doses >220 mg/kg/day. Based on very limited information in literature indicating a potential for possible endocrine disrupting effects of BHA, it is recommended that these possible effects be further evaluated in the future, when sufficient available and reliable data become available to the Agency. Given their metabolism and excretion by the body, typical concentrations of < 0.2% in food-use pesticide products, and long history of use as food additives, no exposures of concern are expected from the use of BHA and BHT as antioxidants in pesticide products.

Taking into consideration all available information on BHA and BHT, EPA has determined there is a reasonable certainty that no harm to any population subgroup will result from aggregate exposure to BHA and BHT when used as inert ingredients in pesticide formulations when considering the dietary exposure and all other non-occupational sources of pesticide exposure for which there is reliable information. Therefore, it is recommended that the four exemptions from the requirement of a tolerance established for residues of BHA and BHT be maintained and considered reassessed as safe under section 408(q) of the FFDCA.

X. Ecotoxicity and Ecological Risk Characterization

According to their physical/chemical properties, BHA and BHT are slightly volatile, BHA is moderately water soluble, and BHT is slightly water soluble. Based on their Log KoW values, neither chemical is likely to bioconcentrate. LC_{50} values for numerous aquatic species were all $\geq$ 5300 μg/L, with most $\geq$ 13,500 μg/L, for BHA exposure and ranged between 870 (rainbow trout) and 65,000 μg/L for BHT exposure (ECOTOX 2005). Aquatic toxicity data for BHT from the OECD SIDS document is summarized below.

Table 3. Aquatic Toxicity Data (OECD SIDS 2002)

Chemical/CAS/ Reference	Acute Fish *(Brachydanio rerio)*	Daphnia *(Daphnia magna)*	Algae *(Scenedesmus subspicatus)*
BHT 128-37-0 (OECD SIDS 2002)	96h $LC_0 \geq 0.57$ mg/L	48h $EC_0 \geq 0.17$ mg/L	72h $E_rC_8 = 0.4$ mg/L Can be used as NOEC

The data from a 1991 special monitoring program of the concentration of BHT in German rivers are listed below (LFU Baden-Wurttemberg 1994 as cited in OECD SIDS 2002).

Rhine: < 0.02-0.09 μg/l (90 percentile 0.08 μg/l)
Danube: < 0.02-0.16 μg/l (90 percentile 0.09 μg/l)
Neckar: < 0.02-0.09 μg/l (90 percentile 0.08 μg/l)

Aquatic toxicity effect levels from exposure to BHA and BHT are in the low ppm range, classifying these chemicals as moderately to slightly toxic to aquatic organisms. Available mammalian data do not indicate an acute concern for terrestrial toxicity for BHA and BHT; however, there may be a potential for reproductive effects in mammals with chronic exposure. Based on the available information and the antioxidant use only of these chemicals in pesticide formulations, with typical concentrations in food-use pesticide products < 0.2%, it is expected that these chemicals are unlikely to present a significant hazard to aquatic and terrestrial organisms from normal use of pesticide products containing BHA and/or BHT.

References:

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U.S. Food and Drug Administration, Center for Drug Evaluation and Research, Inactive Ingredient Search for Approved Drug Products, http://www.accessdata.fda.gov/scripts/cder/iig/index.cfm (8/20/2005).

WHO Food Additives Series 35, Butylated Hydroxytoluene, http://www.inchem.org/documents/jecfa.jecmono/v35je02.htm, 8/22/2005.

APPENDIX A

21 CFR citations from the EAFUS (Everything Added to Food in the United States) Food Additive Database (http://www.cfsan.fda.gov/~dms/eafus.html 8/09/2005)

21 CFR §		BHA	BHT
137.350	Enriched Rice		X
166.110	Margarine	X	X
172.110	Food additives permitted for direct addition to food for human consumption.	X	
172.115	Food additives permitted for direct addition to food for human consumption.		X
172.515	Synthetic flavoring substances and	X	
172.615	Chewing Gum Base	X	X
173.340	Defoaming Agents	X	X
175	Indirect Food Additives: Adhesives and Components of Coatings	X	X
176.170	Components of paper and paperboard in contact with aqueous and fatty foods.	X	X
176.210	Defoaming agents used in the manufacture of paper and paperboard.	X	X
177	Indirect Food Additives: Polymers	X	X
178.2010	Antioxidants and/or stabilizers for polymers.		X
178.3570	Lubricants with incidental food contact.	X	X
179.45	Packaging materials for use during the irradiation of prepackaged foods.	X	X
181.24	Antioxidants	X	X
182.3169	Substances Generally Recognized as Safe – Butylated Hydroxyanisole	X	
182.3173	Substances Generally Recognized as Safe – Butylated Hydroxytoluene		X

APPENDIX B

U.S. Food and Drug Administration Center for Drug Evaluation and Research
Inactive Ingredient Search for Approved Drug Products
(http://www.accessdata.fda.gov/scripts/cder/iig/index.cfm, 8/20/2005)

INACTIVE INGREDIENT	ROUTE; DOSAGE FORM	CAS NUMBER	MAX POTENCY
BUTYLATED HYDROXYANISOLE	INTRAMUSCULAR; INJECTION	008003245	0.03%
BUTYLATED HYDROXYANISOLE	IV(INFUSION); INJECTION	008003245	0.0003%
BUTYLATED HYDROXYANISOLE	IV(INFUSION); POWDER, FOR INJECTION SOLUTION	008003245	
BUTYLATED HYDROXYANISOLE	NASAL; SOLUTION	008003245	2%
BUTYLATED HYDROXYANISOLE	NASAL; SPRAY, METERED	008003245	0.0002%
BUTYLATED HYDROXYANISOLE	ORAL; CAPSULE	008003245	0.08MG
BUTYLATED HYDROXYANISOLE	ORAL; CAPSULE, SOFT GELATIN	008003245	1MG
BUTYLATED HYDROXYANISOLE	ORAL; CONCENTRATE	008003245	0.0075%
BUTYLATED HYDROXYANISOLE	ORAL; EMULSION	008003245	
BUTYLATED HYDROXYANISOLE	ORAL; GRANULE, FOR SUSPENSION	008003245	
BUTYLATED HYDROXYANISOLE	ORAL; SOLUTION	008003245	0.0189%
BUTYLATED HYDROXYANISOLE	ORAL; SUSPENSION	008003245	0.25%

INACTIVE INGREDIENT	ROUTE; DOSAGE FORM	CAS NUMBER	MAX POTENCY
BUTYLATED HYDROXYANISOLE	ORAL; TABLET	008003245	5MG
BUTYLATED HYDROXYANISOLE	ORAL; TABLET, FILM COATED	008003245	0.4MG
BUTYLATED HYDROXYANISOLE	RECTAL; SUPPOSITORY	008003245	0.213MG
BUTYLATED HYDROXYANISOLE	SUBLINGUAL; TABLET	008003245	0.5MG
BUTYLATED HYDROXYANISOLE	TOPICAL; EMULSION, CREAM	008003245	0.1%
BUTYLATED HYDROXYANISOLE	TOPICAL; GEL	008003245	0.05%
BUTYLATED HYDROXYANISOLE	TOPICAL; LOTION	008003245	
BUTYLATED HYDROXYANISOLE	TOPICAL; OINTMENT	008003245	0.005%
BUTYLATED HYDROXYANISOLE	TOPICAL; SOLUTION	008003245	
BUTYLATED HYDROXYANISOLE	VAGINAL; EMULSION, CREAM	008003245	0.125%
BUTYLATED HYDROXYANISOLE	VAGINAL; OINTMENT	008003245	0.02%
BUTYLATED HYDROXYANISOLE	VAGINAL; SUPPOSITORY	008003245	1MG

INACTIVE INGREDIENT	ROUTE; DOSAGE FORM	CAS NUMBER	MAX POTENCY
BUTYLATED HYDROXYTOLUENE	BUCCAL; GUM, CHEWING	000128370	0.21MG
BUTYLATED HYDROXYTOLUENE	INHALATION; LIQUID	000128370	
BUTYLATED HYDROXYTOLUENE	INTRAMUSCULAR; INJECTION	000128370	0.03%
BUTYLATED HYDROXYTOLUENE	INTRAVENOUS; POWDER, FOR INJECTION SOLUTION, LYOPHILIZED	000128370	0.0015%
BUTYLATED HYDROXYTOLUENE	IV(INFUSION); INJECTION	000128370	0.001%
BUTYLATED HYDROXYTOLUENE	IV(INFUSION); POWDER, FOR INJECTION SOLUTION	000128370	
BUTYLATED HYDROXYTOLUENE	NASAL; SPRAY, METERED	000128370	0.01%
BUTYLATED HYDROXYTOLUENE	ORAL; CAPSULE	000128370	0.2MG
BUTYLATED HYDROXYTOLUENE	ORAL; CAPSULE, SOFT GELATIN	000128370	0.25MG
BUTYLATED HYDROXYTOLUENE	ORAL; SOLUTION	000128370	0.0189%
BUTYLATED HYDROXYTOLUENE	ORAL; SOLUTION, LIQUID, CONCENTRATE, ORAL	000128370	0.01%
BUTYLATED HYDROXYTOLUENE	ORAL; TABLET	000128370	0.4MG
BUTYLATED HYDROXYTOLUENE	ORAL; TABLET, CONTROLLED RELEASE	000128370	0.21MG
BUTYLATED HYDROXYTOLUENE	ORAL; TABLET, EXTENDED RELEASE	000128370	

INACTIVE INGREDIENT	ROUTE; DOSAGE FORM	CAS NUMBER	MAX POTENCY
BUTYLATED HYDROXYTOLUENE	ORAL; TABLET, SUSTAINED ACTION	000128370	0.24MG
BUTYLATED HYDROXYTOLUENE	RECTAL; SUPPOSITORY	000128370	0.213MG
BUTYLATED HYDROXYTOLUENE	TOPICAL; CREAM, AUGMENTED	000128370	0.05%
BUTYLATED HYDROXYTOLUENE	TOPICAL; CREAM, EMULSION, SUSTAINED RELEASE	000128370	0.1%
BUTYLATED HYDROXYTOLUENE	TOPICAL; EMULSION, CREAM	000128370	0.1%
BUTYLATED HYDROXYTOLUENE	TOPICAL; GEL	000128370	2%
BUTYLATED HYDROXYTOLUENE	TOPICAL; OINTMENT	000128370	0.025%
BUTYLATED HYDROXYTOLUENE	TOPICAL; SHAMPOO	000128370	0.1%
BUTYLATED HYDROXYTOLUENE	TOPICAL; SOLUTION	000128370	0.088%
BUTYLATED HYDROXYTOLUENE	TOPICAL; SWAB	000128370	
BUTYLATED HYDROXYTOLUENE	VAGINAL; EMULSION, CREAM	000128370	0.05%
BUTYLATED HYDROXYTOLUENE	VAGINAL; SUPPOSITORY	000128370	

FDA/Center for Drug Evaluation and Research
Office of Generic Drugs
Division of Labeling and Program Support
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