

# **Bridged Alkyl Phenols**

## **Category Justification and Testing Rationale**

CAS Nos.: 96-69-5, 85-60-9, 79-96-9, and 7786-17-6  
(Chemical for data purposes: CAS No. 128-37-0)

Rubber and Plastic Additives Panel of  
The American Chemistry Council  
July 2003

---

### **List of Member Companies in the Rubber and Plastic Additives Panel**

The Rubber and Plastic Additives Panel of the American Chemistry Council include the following member companies: Alco Chemical Corporation; Bayer Polymers LLS; Ciba Specialty Chemicals Corporation; Crompton Corporation; Eliokem, Inc.; Flexsys America L.P.; The Goodyear Tire & Rubber Company; The Lubrizol Corporation; Noveon, Inc.; and R.T. Vanderbilt Company Inc.

### **Executive Summary**

The American Chemistry Council's Rubber and Plastic Additives Panel (RAPA), and its member companies, hereby submit a Test Plan and supporting documentation for the Bridged Alkyl Phenols category of chemicals under the Environmental Protection Agency's High Production Volume (HPV) Challenge Program. This submission constitutes a partial revision of documents previously submitted to the Program by the RAPA Panel. In the previous submission, dated December 18, 2001, the Bridged Alkyl Phenols were included in a category called "Hindered Phenols." In comments dated December 5, 2002, EPA noted that "the data provided by the sponsor support the category with respect to the physicochemical, environmental fate and ecotoxicological properties of these substances; the health endpoints are less well supported." Comments received from Environmental Defense (dated May 23, 2002) also noted issues about the "Hindered Phenols" category. Accordingly, revised Test Plans and Robust Summaries for the eight chemicals that comprised the former "Hindered Phenols" category will be submitted as two categories (Styrenated Phenols and Bridged Alkyl Phenols) and two stand-alone chemicals (CAS numbers 68610-51-5 and 27676-62-6).

Bridged Alkyl Phenols are non-staining, non-discoloring, non-migratory additives for natural rubber, synthetic rubber, adhesives, plastics, textile fibers, cable coatings, flooring, and coated paper as well as natural and synthetic oils. Their sole purpose is to prevent or greatly delay the deterioration caused by air oxidation. These phenols are very cost-effective and efficient antioxidants. Usage levels for most applications are typically within the range of 0.5 to 2%. Due to their low volatility and non-migratory nature, many bridged alkyl phenol antioxidants are regulated for use by the Food and Drug Administration (FDA) in a number of food-contact

applications as an Indirect Food Additive or are used as an intermediate in the production of products that have food contact use.

In consideration of animal welfare concerns to minimize the use of animals in the testing of chemicals, the Panel has conducted an extensive literature search for all available data, published and unpublished. It has also performed an analysis of the adequacy of the existing data. Further, it developed a scientifically supportable category of related chemicals and used structure-activity relationship information to address certain data requirements. Based on an assessment of these data, the Panel concluded that sufficient data on the members of this category exist for the purposes of the HPV Program and therefore, no additional testing is recommended.

### **Bridged Alkyl Phenols Category**

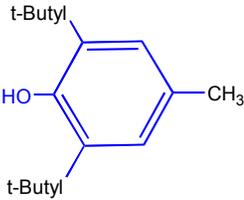
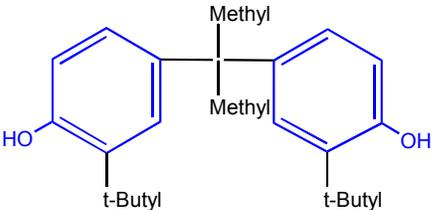
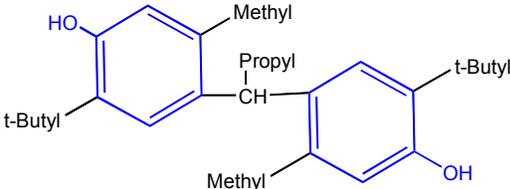
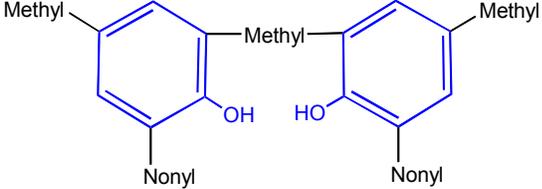
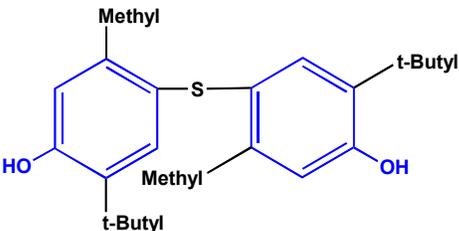
As defined by EPA under the HPV Program, a chemical category is “a group of chemicals whose physicochemical and toxicological properties are likely to be similar or follow a regular pattern as a result of structural similarity.” The similarities should be based on a common functional group, common precursors or breakdown products (resulting in structurally similar chemicals) and an incremental and constant change across the category. The goal of developing a chemical category is to use interpolation and/or extrapolation to assess chemicals rather than conducting additional avoidable testing with specific consideration of animal welfare concerns to minimize the use of animals in the testing of chemicals.

Relying on several factors specified in EPA’s guidance document on “Development of Chemical Categories in the HPV Challenge Program,”<sup>1</sup> in which use of chemical categories is encouraged, the related chemicals discussed below constitute a chemical category.

**Structural Similarity:** The Bridged Alkyl Phenols Category consists of a group of chemicals in which two molecules of mono or di-substituted alkyl (C1, C4, and/or C9) phenols are “bridged” or linked by a single atom (carbon or sulfur). The carbon atom linking the alkyl phenol groups contains hydrogen, propyl, or methyl substitutions. CAS No. 128-37-0 (BHT) is included in this category for data purposes because it is an alkyl phenol with a single carbon group such as the ones that link the phenol groups for the sponsored HPV chemicals. BHT was considered in 2001, under the sponsorship of Germany and Bayer AG and ACC’s BHT Panel, in the Organization for Economic Cooperation and Development (OECD) Screening Information Data Set (SIDS)/International Council of Chemical Associations (ICCA) program. The structural similarities of the four sponsored HPV chemicals and the data-rich surrogate (BHT) are described below.

---

<sup>1</sup> US EPA, Office of Pollution Prevention and Toxics. Development of Chemical Categories, Chemical Right-to-Know Initiative. <http://www.epa.gov/opptintr/chemrtk/categuid.htm>.

<p><b>2,6-Di-tert-butyl-p-cresol (BHT) (128-37-0)</b></p> 	<p><b>Phenol, 4,4'-(1-methylethylidene)bis [2-(1,1-dimethylethyl)]-, (79-96-9)</b></p> 
<p><b>4,4'-Butylidenebis(6-t-butyl-m-cresol) (85-60-9)</b></p> 	<p><b>Phenol, 2,2'-methylenebis(4-methyl-6-nonyl) (7786-17-6)</b></p> 
<p><b>4,4'-Thiobis-6-(t-butyl-m-cresol) (96-69-5)</b></p> 	

**Similarity of Physicochemical Properties:** The bridged alkyl phenols are solids at room temperature. The vapor pressure of these chemicals is low. Generally, the water solubility for the group chemicals is low and the partition coefficients are high.

While appreciating EPA's suggestion that boiling points be determined for these chemicals, after consideration, the Panel concluded available evidence shows that the calculated values are adequate and valid estimates of this end-point. The boiling point for the surrogate, BHT, is 265°C compared to the calculated values of 433°C to 584°C. CAS No. 96-69-5 and CAS No. 85-60-9 decompose before boiling at 207.4°C and 282°C, respectively. Because these HPV chemicals are larger molecules than BHT, their boiling point would be expected to be higher. Therefore, the calculated numbers appear to be valid and to provide sufficient information for the purposes of the HPV Program.

**Fate and Transport Characteristics.** Experimental data show that bridged alkyl phenols are not readily biodegradable. The low water solubility of these chemicals precludes experimentally obtaining hydrolysis data. Model-derived photodegradation indicates that these substances photodegrade rapidly. Fugacity modeling shows that, generally, partitioning would be to soil and sediments rather than air or water. Modeling has been done for all of the substances where the model could be applied and bridging can be done to those substances where the model was not suitable. Additional modeling for the members of this category is not recommended for the purposes of the HPV Program.

The EPA recommended photodegradation testing for CAS No. 85-60-9, measured biodegradation data on CAS No. 7786-17-6, and additional discussion/explanation of the slow degradation of CAS No. 96-69-0.

- **Photodegradation:** The Panel believes that the data on the surrogate chemical, BHT, combined with the calculated values for all chemicals are adequate. These data indicate that photodegradation is rapid. The somewhat shorter  $t_{1/2}$  values for the sponsored HPV chemicals compared with the surrogate appears to be consistent with the greater number of reactive sites (functional groups) for the sponsored HPV chemicals. Therefore, the data are considered valid and adequate for the HPV Program and do not support a recommendation that a photodegradation study be conducted on CAS No. 85-60-9.
- **Biodegradation/water solubility:** The Panel believes that the data on the surrogate, BHT, combined with the calculated values for all chemicals is adequate for the HPV Program. The physicochemical data indicate that these chemicals are poorly soluble in water, which is consistent with their molecular weight. Such poorly soluble/high molecular weight chemicals would not be expected to be readily bioavailable and, therefore, not readily biodegradable. The data for chemicals in the category are consistent and do not support a recommendation for further testing on CAS No. 96-69-5 or CAS No. 7786-17-5.

**Toxicological Similarity.** Review of existing published and unpublished test data for the bridged alkyl phenols shows that the aquatic and mammalian toxicity among the substances in this category are similar.

**Aquatic Toxicology.** Bridged alkyl phenols have low water solubility and, therefore, low aquatic toxicity. Experimental data are available on acute fish toxicity, acute invertebrate toxicity, and alga toxicity for the majority of chemicals in this category. Data can be bridged to those substances without experimental data. No additional ecotoxicity testing is proposed for the purposes of the HPV Program. However, additional clarifying information has been added to the robust summaries.

**Mammalian Toxicology - Acute.** Acute oral and dermal toxicity data are available for all but two of the substances in the group. The data show that acute toxicity of these substances is low. The testing for acute toxicity spans five decades. While the older studies may not be to current guidelines, tests done according to recent guidelines and

under GLP confirm the conclusions of the earlier testing. No additional acute toxicity testing is proposed for the purposes of the HPV Program. However, additional clarifying information has been added to the robust summaries.

**Mammalian Toxicology - Mutagenicity.** Data from bacterial reverse mutation assays and *in vitro* and *in vivo* chromosome aberration studies were reviewed. Adequate bacterial gene mutation assays have been conducted with all of the category chemicals except two. Chromosome aberration studies, *in vitro* and/or *in vivo*, are available for all but two substances. The mutagenicity data span the range of structures and molecular weights and data can be bridged from other members of the group to meet any outstanding requirements. The weight of evidence for mutagenic potential for this category indicates these substances are not mutagenic. The category has been adequately tested for mutagenicity to meet requirements of the HPV Program, therefore, no additional mutagenicity testing is proposed. However, additional clarifying information has been added to the robust summaries.

**Mammalian Toxicology – Repeated Dose Toxicity.** Repeated dose toxicity data of approximately three months (90-day, 12- and 13-week) are available for most substances in this group. Data on repeated dose toxicity were not identified for three substances within the larger hindered phenols category. Reliable chronic toxicity/carcinogenicity studies have been done on two of the group members. Adequate data span the range of structures and molecular weights and available data can be bridged from other members of the group. Sufficient data are available for meeting the requirements of repeated dose toxicity of the hindered phenols for the purposes of the HPV Program. However, additional clarifying information has been added to the robust summaries.

**Mammalian Toxicology - Reproductive and Developmental Toxicity.** For the majority of the hindered phenol chemicals some evaluation of effects on reproduction or reproductive organs is available. Multi-generation reproduction studies are available for three of the substances in this group. Evaluation of effects on reproduction for four of the hindered phenols is provided by histopathological data on male and female reproductive organs from the repeated dose toxicity studies. Developmental toxicity data exist for two of the substances included in this group. Available data for reproductive and developmental toxicity span the range of structures and molecular weights and can be bridged to those group members where data have not been identified. No additional testing is proposed for the purposes of the HPV Program. However, additional clarifying information has been added to the robust summaries.

**Conclusion.** Based on the data reviewed in this document, the physicochemical and toxicological properties of the proposed bridged alkyl phenols Category are similar and follow a regular pattern as a result of that structural similarity. Therefore, the EPA's definition of a chemical category has been met for the 5 chemicals in the Bridged Alkyl Phenols Category, and the Panel proposes no additional testing for the purposes of the HPV Program.

## Introduction

A provision for the use of structure activity relationships (SAR) to reduce testing needs is included under EPA's HPV Program. Specifically, categories may be formed based on structural similarity, through analogy, or through a combination of category and analogy for use with single chemicals. The benefits of using a category approach are numerous. They include the accelerated release of hazard information to the public (category analysis and testing are proposed to be initiated within the first two years of the HPV Program); a reduction in the number of animals used for testing; and an economic savings as a result of a reduced testing program.

The five chemicals that form the bridged alkyl phenols category based on structural similarity are:

- 2,6-Di-tert-butyl-p-cresol (CAS No. 128-37-0; data-rich surrogate)
- 4,4'-Butylidenebis(6-t-butyl-m-cresol) (CAS No. 85-60-9)
- Phenol, 4,4'-(1-methylethylidene)bis[2,(1,1-dimethylethyl)]- (CAS No. 79-96-9)
- Phenol, 2,2'-methylenebis(4-methyl-6-nonyl) (CAS No. 7786-17-6)
- 4,4'-Thiobis-6-(t-butyl-m-cresol) (CAS No. 96-69-5)

The development of this category follows current EPA guidelines.

## Background Information: Manufacturing and Commercial Applications

### Manufacturing

A typical manufacturing process for a bridged alkyl phenol antioxidant uses a substituted cresol raw material for the phenolic ring portion of the molecule, and an aldehyde raw material for the bridging or connecting group. The batch reaction takes place in an alcoholic solvent and utilizes an acid catalyst. When the reaction is complete, the batch is quenched with water and decanted. Purification steps may include additional water washes/decants before the product is slurried with a hydrocarbon solvent, vacuum filtered, washed with additional solvent, centrifuged and dried.

### Commercial Applications

Bridged alkyl phenols are non-staining, non-discoloring, non-migratory additives for natural rubber, synthetic rubber, adhesives, plastics, textile fibers, cable coatings, flooring, and coated paper, as well as natural and synthetic oils. Their purpose is to prevent or greatly delay the deterioration caused by air oxidation. Using a bridged alkyl phenol antioxidant greatly extends the useful life of a transparent, translucent, white or light-colored article by preventing the formation of surface cracks, brittleness and yellowing. In oils, a bridged alkyl phenol antioxidant functions as a stabilizer by extending the useful life of the lubricating fluid by slowing the natural breakdown process and limiting the buildup of tars and residues. The overall

Category Justification and Testing Rationale  
Bridged Alkyl Phenols Category

---

mechanism is similar to that of the antioxidant vitamins A and E in the human body – bridged alkyl phenol antioxidants serve as free-radical scavengers.

Bridged alkyl phenols are cost-effective and efficient antioxidants. Usage levels for most applications are typically within the range of 0.5 to 2%.

Due to their low toxicity, low volatility and non-migratory nature, many bridged alkyl phenols are regulated for use by the Food and Drug Administration (FDA) in a number of food-contact applications as an Indirect Food Additive or are an intermediate in the production of products that are used in food contact applications:

<b>FDA Regulation</b>	<b>Application</b>	<b>CAS Nos.</b>
175.105	Components of Adhesives	85-60-9, 96-69-5, 7786-17-6
175.300	Resinous and Polymeric Coatings	85-60-9
177.1632	Poly(phenyleneterephthalamide) Resins	85-60-9
177.2600	Rubber Articles – Antioxidants	85-60-9, 96-69-5, 7786-17-6
178.2010	Antioxidants and/or Stabilizers for Polymers	85-60-9, 96-69-5, 7786-17-6

2,6-Di-tert-butyl-p-cresol (CAS No. 128-37-0) (butylated hydroxytoluene or BHT), the prototype molecule for the hindered phenol antioxidants, is Generally Recognized As Safe (GRAS) by the Food and Drug Administration, and is approved for use as a direct food additive and preservative for numerous food products.

### **Shipping/Distribution**

Many of the bridged alkyl phenols are manufactured in North America, Europe and Asia by more than a dozen different companies. They are shipped worldwide for use at manufacturing sites engaged in the production of rubber and plastic articles and mechanical goods, food containers and food handling equipment, industrial oils and lubricants, synthetic fabrics and specialized papers.

### **Worker/Consumer Exposure**

The rubber and plastics additives industry has a long safety record and sophisticated industrial users handle these materials. Exposure of workers handling bridged alkyl phenols is likely to be greater in the area of material packaging rather than from chemical manufacturing. These materials are made as powders, flakes, emulsions and liquids. Product forms that minimize dust generation, coupled with the mechanized materials handling systems of the large industrial users, combine to keep exposures to minimum levels. However, during material packout at the manufacturing site and, to a lesser degree during weigh-up activities at the customer site, there is a potential for skin and inhalation exposure (nuisance dust is the primary route of worker exposure) and also dermal contact with liquid forms.

All known sales of the bridged alkyl phenol antioxidants are to industrial users only. There are no known consumer uses for these materials as manufactured, so there are no expected direct-to-consumer sales. Only very small amounts are used in the manufacture of rubber and plastics or as oil additives, and the materials themselves become bound in the polymer matrix during the rubber and plastic curing process. For these reasons, consumer exposure to bridged alkyl phenol antioxidants is believed to be minimal. Should exposure occur, the most likely route would be skin contact from rubber and plastic articles, or from skin contact with oils.

## Development of the Bridged Alkyl Phenols Category

EPA has described a stepwise process for developing categories. These steps include:

- Grouping a series of like chemicals, including the definition of criteria for the group.
- Gathering data on physicochemical properties, environmental fate and effects, and health effects for each member of the category.
- Evaluating the data for adequacy.
- Constructing a matrix of available and unavailable data.
- Determining whether there is a correlation among category members and data gathered.

### Definition of the Bridged Alkyl Phenols Category

As defined by EPA under the HPV Program, a chemical category is “a group of chemicals whose physicochemical and toxicological properties are likely to be similar or follow a regular pattern as a result of structural similarity.” The similarities should be based on a common functional group, common precursors or breakdown products (resulting in structurally similar chemicals) and an incremental and constant change across the category. The goal of developing a chemical category is to use interpolation and/or extrapolation to assess chemicals rather than conducting additional testing.

The substances to be included in this bridged alkyl phenols category are:

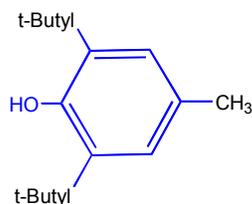
<b>Bridged Alkyl Phenols</b>	
<b>Name</b>	<b>CAS No.</b>
2,6-di-tert-butyl-p-cresol	128-37-0
4,4'-thiobis-6-(t-butyl-m-cresol)	96-69-5
4,4'-butylidenebis(6-t-butyl-m-cresol)	85-60-9
phenol, 4,4'-(1-methylethylidene)bis[2-(1,1-dimethylethyl)]-,	79-96-9
phenol, 2,2'-methylenebis(4-methyl-6-nonyl)	7786-17-6

 = N = Non-sponsored chemical; used for data purposes only

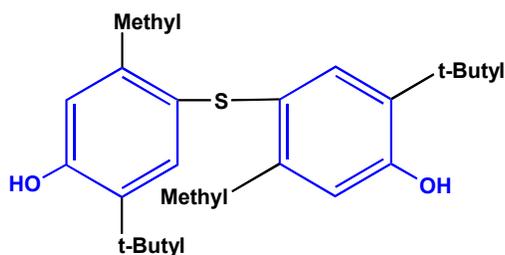
The bridged alkyl phenols category consists of a group of chemicals in which two molecules of mono or di-substituted alkyl (C1, C4, and/or C9) phenols are “bridged” or linked by a single atom (carbon or sulfur). The carbon atom linking the alkyl phenols contains hydrogen, propyl, or methyl substitutions. CAS No. 128-37-0 (BHT) is included in this category for data purposes because it is an alkyl phenol with a single carbon group such as the ones that link the phenol

groups for the other HPV chemicals. Due to the bulky substituent groups, the substances, which may be either room temperature solids or liquids, have limited water solubility, high partition coefficients and are not readily biodegradable.

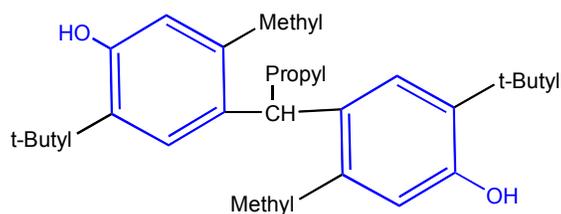
**2,6-di-tert-butyl-p-cresol (128-37-0)** (butylated hydroxytoluene or BHT) is hydroxybenzene with aliphatic tertiary butyl groups adjacent to the hydroxyl (OH) group and a methyl group in the 4- or para- position.



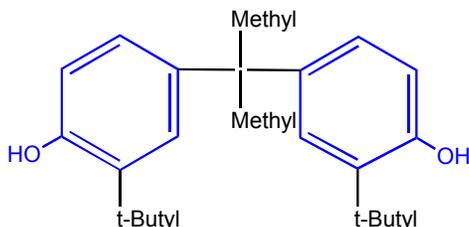
**4,4'-Thiobis-6-(t-butyl-m-cresol) (96-69-5)** is two identically substituted hydroxybenzene groups linked by a sulfur bridge. Relative to BHT, one butyl group adjacent to the hydroxyl group (OH) is absent, and a sulfur bridge adjacent to the methyl groups links the two hydroxybenzene groups in this configuration.



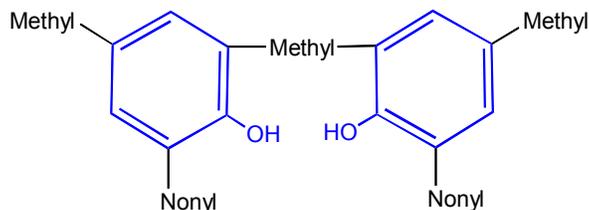
**4,4'-Butylidenebis(6-t-butyl-m-cresol) (85-60-9)**, like 4,4'-thiobis-6-(t-butyl-m-cresol) (96-69-5) is two identically substituted hydroxybenzene groups. In each hydroxybenzene ring one of the aliphatic butyl groups adjacent to the hydroxyl (OH) group is absent and an aliphatic isobutyl group adjacent to the methyl groups links the two rings.



**Phenol, 4,4'-(1-methylethylidene)bis[2-(1,1-dimethylethyl)]-, (79-96-9)** is two identically substituted hydroxybenzene groups linked by an isopropyl group. Compared to BHT, each hydroxybenzene group lacks one of the tertiary butyl groups adjacent to the hydroxyl group and the isopropyl group linking the two aromatic rings replaces the methyl group.



**Phenol, 2,2'-methylenebis(4-methyl-6-nonyl) (7786-17-6)** is two identically substituted hydroxybenzene groups linked by a methyl group. Compared to BHT, in each hydroxybenzene group, one of the aliphatic butyl groups adjacent to the hydroxyl group (OH) is replaced by an aliphatic nonyl group and the other butyl group is replaced by the methyl group linking the two rings.



### **Matrix of SIDS Endpoints**

In order to construct a matrix of SIDS endpoints for the bridged alkyl phenols category, the data on physicochemical properties, environmental fate and effects, and health effects for each member of the category must be collected and evaluated for adequacy. The results of these activities are presented in the tables and text below, providing a matrix of available data for the bridged alkyl phenols.

### **Correlation within the Bridged Alkyl Phenols Category**

The matrix data patterns for physicochemical properties; environmental fate, ecotoxicity; and health effects have been evaluated for the members of the bridged alkyl phenols category. A description of the results of this evaluation follows.

### **Correlation of Physicochemical Properties**

The physicochemical properties of the members of the bridged alkyl phenols category are presented in Table 1. These materials may exist as liquids or solids at room temperature. The similarities in the other physicochemical properties of these materials, which are described below, provide justification of this group of chemicals as a category within the HPV Challenge Program. The vapor pressure and water solubility of these chemicals is low, the partition coefficient is high.

Experimentally determined melting points are available for all but one of the bridged alkyl phenols. Model calculated melting and boiling points are provided for those two and are consistent with the experimentally determined value for BHT (128-37-0). CAS No. 96-69-5 and CAS No. 85-60-9 decompose before boiling at 207.4°C and 282°C, respectively.

Experimentally determined or model calculated vapor pressures are available for all of the group chemicals. Model calculated vapor pressures are consistent with the experimentally determined values.

Experimentally determined water solubility is reported for three of the group chemicals. These can be used to extrapolate to the other members of the group. Water solubility data for 2,6-di-tert-butyl-p-cresol (128-37-0), 4,4'-Thiobis-6-(t-butyl-m-cresol) (96-69-5), and 4,4'-butylidenebis(6-t-butyl-m-cresol) (85-60-9) can be bridged to phenol, 4,4'-(1-methylethylidene)bis[2-(1,1-dimethylethyl)]-, (79-96-9) and phenol, 2,2'-methylenebis(4-methyl-6-nonyl) (7786-17-6).

Experimentally determined partition coefficients are available for 2,6-di-tert-butyl-p-cresol (128-37-0). Model calculated partition coefficients are available for all of the other substances in this category and are consistent with the experimentally determined values.

Experimental or model calculated physiochemical data are available for all chemicals in the category. The model calculated values are consistent with the experimentally determined data. It is concluded that there are adequate data for physicochemical properties for the bridged alkyl phenols for the purposes of the HPV Program.

### **Correlation of Environmental Fate**

Data on environmental fate for the substances in the bridged alkyl phenols category are presented in Table 2. The bridged alkyl phenols are not readily biodegradable, but have rapid photodegradation. As a result of the low water solubility of these chemicals, hydrolysis data are not available, except for one substance. Fugacity modeling indicates that partitioning would generally be to soil and sediments rather than air or water.

Hydrolysis testing is not possible for the bridged alkyl phenols because of low water solubility. Data were available only for 4,4'-thiobis-6-(t-butyl-m-cresol) (96-69-5), indicating that it is not readily hydrolyzed.

Model derived photodegradation half-lives are presented for all of the category substances. Actual data is included also for the surrogate, BHT (128-37-0).

The bridged alkyl phenols are not readily biodegradable. Biodegradation data are available for all but two of the substances. For phenol, 4,4'-(1-methylethylidene)bis[2-(1,1-dimethylethyl)]-, (79-96-9) and phenol, 2,2'-methylenebis(4-methyl-6-nonyl) (7786-17-6) data can be bridged from 4,4'-butylidenebis(6-t-butyl-m-cresol) (85-60-9) and BHT (128-37-0).

The available data for environmental fate span the range of structures and molecular weights. It is concluded that there are adequate data to evaluate the environmental fate of this group of bridged alkyl phenols for the purposes of the HPV Program.

### **Correlation of Ecotoxicity**

The HPV Challenge Program requires an acute aquatic ecotoxicity test in fish, invertebrates, and algae. The substances in the bridged alkyl phenols category have low water solubility and this is reflected in low aquatic toxicity. The data for ecotoxicity are summarized in Table 3.

#### Acute fish toxicity

Fish 96-hour LC50 data are available for all of the chemicals, except phenol, 4,4'-(1-methylethylidene)bis[2-(1,1-dimethylethyl)]-, (79-96-9) and phenol, 2,2'-methylenebis(4-methyl-6-nonyl) (7786-17-6). It would be expected that acute fish toxicity of phenol, 4,4'-(1-methylethylidene)bis[2-(1,1-dimethylethyl)]-, (79-96-9) and phenol, 2,2'-methylenebis(4-methyl-6-nonyl) (7786-17-6) would be similar to 4,4'-butylidenebis(6-t-butyl-m-cresol) (85-60-9). It is concluded that there are adequate data to evaluate the acute toxicity to fish for this group of chemicals with limited water solubility for the purposes of the HPV Program.

#### Acute Invertebrate Toxicity

Acute toxicity data for Daphnia are available for 2,6-di-tert-butyl-p-cresol (128-37-0); 4,4'-thiobis-6-(t-butyl-m-cresol) (96-69-5); and 4,4'-butylidenebis(6-t-butyl-m-cresol) (85-60-9). As with acute fish toxicity, the toxicity in Daphnia is limited by the water solubility of the chemicals. The data for acute invertebrate toxicity span the range of structures and molecular weights. It is concluded that there are adequate data to evaluate the acute toxicity to invertebrates for the purposes of the HPV Program.

### Algal Growth Inhibition

Algal growth inhibition tests are available for 2,6-di-tert-butyl-p-cresol (128-37-0); 4,4'-thiobis-6-(t-butyl-m-cresol) (96-69-5); and 4,4'-butylidenebis(6-t-butyl-m-cresol) (85-60-9). The data for algal growth inhibition span the range of structures and molecular weights. It is concluded that there are adequate data to evaluate the acute toxicity to invertebrates for the purposes of the HPV Program.

### **Correlation of Health Effects**

#### Acute Mammalian Toxicity

The acute toxicity of the bridged alkyl phenols category is summarized in Table 4. Acute oral and dermal toxicity data are available for all, but two, of the substances in the group. The data show that the acute toxicity of the bridged alkyl phenols is low. The testing for acute toxicity spans five decades. While the majority of studies may not be to current guidelines, tests done according to recent guidelines and under GLP confirm the conclusions of the earlier testing. No additional testing is necessary for the purposes of the HPV Program.

#### Genotoxicity

A summary of the mutagenicity testing for the bridged alkyl phenols category is presented in Table 5. The weight of evidence for mutagenic potential for this category indicates these substances are not mutagenic.

**Bacterial Gene Mutation Assays.** Adequate bacterial gene mutation assays have been conducted with all of the category chemicals, except phenol, 4,4'-(1-methylethylidene)bis[2-(1,1-dimethylethyl)]-, (79-96-9), and phenol, 2,2'-methylenebis(4-methyl-6-nonyl) (7786-17-6). A yeast assay (nonbacterial) is available for 4,4'-thiobis-6-(t-butyl-m-cresol) (96-69-5). All assays, with and without metabolic activation, were negative. It is concluded that this group of substances has been adequately tested for gene mutations for the purposes of the HPV Program.

**Chromosome Aberration Studies.** Chromosome aberration studies, in vitro and/or in vivo, are available for all but two of the bridged alkyl phenols in this group. They are phenol, 4,4'-(1-methylethylidene)bis[2-(1,1-dimethylethyl)]-, (79-96-9), and (p-cresol, 2,2'-methylenebis[6-nonyl]) (7786-17-6). With one exception all tests for chromosome aberrations are negative. It is concluded that this group of chemicals has been adequately tested for clastogenic potential for the purposes of the HPV Program.

***In Vitro* Chromosome Aberration Studies.** *In vitro* chromosome aberration studies are available for 2,6-di-tert-butyl-p-cresol (128-37-0), 4,4'-thiobis-6-(t-butyl-m-cresol) (96-69-5), and 4,4'-butylidenebis(6-t-butyl-m-cresol) (85-60-9). All except 2,6-di-tert-butyl-p-cresol were negative.

***In Vivo* Chromosome Aberration Studies.** *In vivo* studies evaluating the potential for chromosome damage are available for two of the bridged alkyl phenols. All *in vivo* evaluations were negative. Multiple studies have been done with 2,6-di-tert-butyl-p-cresol (128-37-0). Micronucleus tests are available for 4,4'-thiobis-6-(t-butyl-m-cresol) (96-69-5). *In vivo* chromosome aberration studies are also available for BHT (128-37-0).

### Repeated Dose Toxicity

A summary of the repeated dose toxicity data for the Bridged Alkyl Phenols Category is presented in Table 6. These repeat dose studies on the members of this category include both subchronic and chronic exposures. The liver is identified as the target organ in rats for all of the substances tested. NOAEL's or NOEL's in rats for 13-week studies ranged from 100 ppm (approximately 5 mg/kg/day) to 500 ppm (approximately 25 mg/kg/day) while NOAEL's or NOEL's in rats for chronic studies were the same, 25 mg/kg/day (500 ppm).

The mutagenicity data combined with the animal data plus the long historical use of BHT (128-37-0) indicate that the chemicals in this class are not expected to exhibit any significant potential to cause cancer. The weight of the evidence indicates that these chemicals are not genotoxic. In chronic studies with 2,6-di-tert-butyl-p-cresol (128-37-0) effects were limited to adenomas of the liver at high doses; no effects were observed at 25 mg/kg/day. No evidence of cancer was noted in mice or rats following two years feeding with 4,4'-Thiobis-6-(t-butyl-m-cresol) (96-69-5), but the kidney was identified as a target organ in female rats. Other target organs are kidney and mesenteric lymph nodes in 4,4'-thiobis-6-(t-butyl-m-cresol) (96-69-5).

Two of the category substances, phenol, 4,4'-(1-methylethylidene)bis[2-(1,1-dimethylethyl)]-, (79-96-9) and phenol, 2,2'-methylenebis(4-methyl-6-nonyl) (7786-17-6), did not offer repeat dose toxicity data. However, the range of structures, molecular weights, and chemistry of the category encompasses both of these chemicals. Therefore, the repeated dose data that currently exists for the members of this category are adequate to predict the toxicity of all the members for HPV purposes. No further testing is proposed.

### Reproductive and Developmental Toxicity

A summary of the reproductive and developmental toxicity data for the bridged alkyl phenols category is presented in Table 7.

**Reproductive Toxicity.** Reproduction studies were identified for 2,6-di-tert-butyl-p-cresol (128-37-0) and 4,4'-thiobis-6-(t-butyl-m-cresol) (96-69-5). In a multi-generation reproduction study with 2,6-di-tert-butyl-p-cresol (128-37-0) non-adverse/non-toxicologically significant effects, increased pup weights were evident at the lowest doses tested. A postnatal mouse screening test with 4,4'-Thiobis-6-(t-butyl-m-cresol) (96-69-5) also was conducted by NTP using a single dose. Increased maternal mortality and decreased pup survival were reported.

Evaluation of effects on reproduction for the bridged alkyl phenols is supplemented by histopathological data on male and female reproductive organs in repeated dose studies. There is

a 90-day study with 4,4'-butylidenebis(6-t-butyl-m-cresol) (85-60-9). A two-year chronic feeding study provides data for 4,4'-thiobis-6-(t-butyl-m-cresol) (96-69-5). No adverse effects were noted on reproductive organs.

No data for the assessment of reproductive toxicity are available for two of the bridged alkyl phenols chemicals: phenol, 4,4'-(1-methylethylidene)bis[2-(1,1-dimethylethyl)]-, (79-96-9) and (p-cresol, 2,2'-methylenebis[6-nonyl] (7786-17-6).

The data on the effects of bridged alkyl phenols on reproduction and reproductive organs span the range of structures and molecular weights. While not all of the data for reproductive effects are from reproduction studies, microscopic evaluations of reproductive organs along with other short-term tests for reproductive effects provide adequate data to evaluate the effects of these bridged alkyl phenols on reproduction for the purposes of the HPV Program.

**Developmental Toxicity.** Developmental studies have been conducted in rats, rabbits, and/or mice with 2,6-di-tert-butyl-p-cresol (128-37-0) and 4,4'-thiobis-6-(t-butyl-m-cresol) (96-69-5). The available data span the range of structures and molecular weights and provide adequate data to evaluate the effects of these bridged alkyl phenols on development for the purposes of the HPV Program.

## Conclusion

The five bridged alkyl phenols meet the EPA definition of a chemical category. The bridged alkyl phenols category consists of a group of chemicals in which two molecules of mono or di-substituted alkyl (C1, C4, and/or C9) phenols are “bridged” or linked by a single atom (carbon or sulfur). The carbon atom linking the alkyl phenols contains hydrogen, propyl, or methyl substitutions. CAS No. 128-37-0 (BHT) is included in this category for data purposes because it is an alkyl phenol with a single carbon group such as the ones that link the phenol groups for the other HPV chemicals. Because of the bulky substituent groups, the substances have limited water solubility, high partition coefficients and are not readily biodegradable. Therefore, the EPA’s definition of a chemical category has been met.

The test plan for the bridged alkyl phenols category was developed giving careful consideration to the number of animals that would be required for any tests that are not available for certain members of the category and whether these additional tests would provide useful and relevant information. The test plan is summarized in Table 8. It is concluded that there are sufficient data on the members of this category for the purposes of the HPV Program and therefore, no additional testing is recommended.

**Table 1.**  
**Matrix of Available and Adequate Data for the Bridged Alkyl Phenols Category**

### Physicochemical Properties

Name (CAS No.)	Molecular Weight	Melting Point °C	Boiling Point °C	Vapor Pressure (mm Hg)	Water Solubility (mg/L)	Partition Coefficient
2,6-di-tert-butyl-p-cresol (128-37-0)	220.36	70	265	0.0225 at 25 °C	0.4 at 20 °C 1.1 at 20 °C	5.1
4,4'-thiobis-6-(t-butyl-m-cresol) (96-69-5)	358.58	156 - 158	NA	$6.3 \times 10^{-7}$ at 70 °C	<0.1 at 25 °C	8.24 (calculated)
4,4'-butylidenebis(6-t-butyl-m-cresol) (85-60-9)	382.64	210	NA	$5.26 \times 10^{-11}$ at 25 °C (calculated)	<0.1 at 18 °C	9.09 (calculated)
phenol, 4,4'-(1-methylethylidene)bis[2-(1,1-dimethylethyl)]-, (79-96-9)	340.51	113-115.5	433 (calculated)	$1.18 \times 10^{-9}$ at 25 °C (calculated)	ND	7.46 (calculated)
phenol, 2,2'-methylenebis(4-methyl-6-nonyl) (7786-17-6)	480.78	252 (calculated)	584 (calculated)	$6.25 \times 10^{-15}$ at 25 °C (calculated)	ND	13.10 (calculated)

ND - No data found

NA – Not Applicable; CAS No. 96-69-5 and CAS No. 85-60-9 decompose before boiling at 207.4°C and 282°C, respectively.

N = Non-sponsored chemical; used for data purposes only

**Table 2**  
**Matrix of Available and Adequate Data for the Bridged Alkyl Phenols Category**

**Environmental Fate**

Name (CAS No.)	Hydrolysis	Photo-degradation (t1/2)	Bio-degradation	Environmental Transport
2,6-di-tert-butyl-p-cresol (128-37-0)	ND	25.2% remained after 8 days  17 hr (EPIWIN)	Aerobic approximately 10% after 56 days; 4.5% after 28 days.	Primarily in air (Mackay, Level I model) Adsorbs to river sediments from water.
4,4'-thiobis-6-(t-butyl-m-cresol) (96-69-5)	>168 hrs at pH 7 at 23 °C	1 hr (EPIWIN)	Aerobic 11% after 90 days	Primarily soil and sediments. (Level III Fugacity Model)
4,4'-butylidenebis(6-t-butyl-m-cresol) (85-60-9)	ND	0.6 hr (EPIWIN)	Aerobic 0-5% after 35 days	Primarily soil and sediments. (Level III Fugacity Model)
phenol, 4,4'-(1-methylethylidene)bis[2-(1,1-dimethylethyl)]-, (79-96-9)	ND	1.3 hr (EPIWIN)	ND	Primarily soil and sediments. (Level III Fugacity Model)
phenol, 2,2'-methylenebis(4-methyl-6-nonyl) (7786-17-6)	ND	1.9 hr (EPIWIN)	ND	Primarily soil and sediments. (Level III Fugacity Model)

ND - No data found

N = Non-sponsored chemical; used for data purposes only

**Table 3.**  
**Matrix of Available and Adequate Data for the Bridged Alkyl Phenols Category**

**Ecotoxicity**

<b>Name (CAS No.)</b>	<b>Acute Fish 96-hr LC50 (mg/L)</b>	<b>Acute Invertebrate 48-hr EC50 (mg/L)</b>	<b>Algal Growth Inhibition EC50 (mg/L)</b>
2,6-di-tert-butyl-p-cresol (128-37-0)	> 0.57	>.31	0.42
4,4'-thiobis-6-(t-butyl-m-cresol) (96-69-5)	0.13 - 0.16 trout 0.24 - 0.51 bluegill 0.14 - 0.36 minnow	0.70	126
4,4'-butylidenebis(6-t-butyl-m-cresol) (85-60-9)	> 1000 in trout, blue gill and minnow	16	> 1000
phenol, 4,4'-(1-methylethylidene)bis[2-(1,1-dimethylethyl)]-, (79-96-9)	ND	ND	ND
phenol, 2,2'-methylenebis(4-methyl-6-nonyl) (7786-17-6)	ND	ND	ND

ND - No data found

N = Non-sponsored chemical; used for data purposes only

**Table 4.**  
**Matrix of Available and Adequate Data for the Bridged Alkyl Phenols Category**

**Acute Toxicity**

<b>Name (CAS No.)</b>	<b>Acute Oral (mg/kg)</b>	<b>Acute Dermal (mg/kg)</b>
2,6-di-tert-butyl-p-cresol (128-37-0)	> 2930	> 2000
4,4'-thiobis-6-(t-butyl-m-cresol) (96-69-5)	4150	>5010
4,4'-butylidenebis(6-t-butyl-m-cresol) (85-60-9)	> 7940	> 7940
phenol, 4,4'-(1-methylethylidene)bis[2-(1,1-dimethylethyl)]-, (79-96-9)	ND	ND
phenol, 2,2'-methylenebis(4-methyl-6-nonyl) (7786-17-6)	ND	ND

ND - No data found

 = Non-sponsored chemical; used for data purposes only

**Table 5.**  
**Matrix of Available and Adequate Data for the Bridged Alkyl Phenols Category**

**Genotoxicity**

Name (CAS No.)	Bacterial Gene Mutation	Chromosomal Aberrations	
		In vitro	In vivo
2,6-di-tert-butyl-p-cresol (128-37-0)	negative	positive	negative
4,4'-thiobis-6-(t-butyl-m-cresol) (96-69-5)	negative	negative	negative
4,4'-butylidenebis(6-t-butyl-m-cresol) (85-60-9)	negative	negative	ND
phenol, 4,4'-(1-methylethylidene)bis[2-(1,1-dimethylethyl)]-, (79-96-9)	ND	ND	ND
phenol, 2,2'-methylenebis(4-methyl-6-nonyl) (7786-17-6)	ND	ND	ND

ND - No data found

N = Non-sponsored chemical; used for data purposes only

**Table 6.**  
**Matrix of Available and Adequate Data for the Bridged Alkyl Phenols Category**  
**Repeated dose Toxicity**

Name (CAS No.)	Subchronic Toxicity	Chronic Toxicity
2,6-di-tert-butyl-p-cresol (128-37-0)	Oral toxicity in rats from 2-gen repro study. F1 gen evaluated at 4 wks and at 6, 11, 16, and 22 mo. NOAEL 25 mg/kg/day	Chronic oral toxicity in rats - 144 wk study. Liver adenomas. NOAEL 25 mg/kg/day
4,4'-thiobis-6-(t-butyl-m-cresol) (96-69-5)	<p>13-week feeding study in rats - Higher ALP and ALT; lower hematocrit and HB conc and RBC; histopath findings in liver (hypertrophy and hyperplasia), kidney (renal cortical tubule effects), and mesenteric lymph nodes (increased size and number of macrophages). NOEL = 500 ppm; LOEL = 1000 ppm</p> <p>13-week feeding study in mice - Higher ALP and ALT; effects on hematocrit, HB conc and RBC; histopath findings in liver (hypertrophy and hyperplasia) and mesenteric lymph nodes (increased size and number of macrophages). NOEL = 250 ppm; LOEL = 500 ppm</p>	<p>Two-year feeding study in rats - Higher AP, ALT and sorbitol dehydrogenase; lower hematocrit, HB conc, and RBC counts; histopath findings in liver; increased severity of nephropathy in females. Not carcinogenic. NOEL = 500; ppm LOEL = 1000 ppm</p> <p>Two-year feeding study in mice - Higher AP and bilirubin; lower hematocrit, HB conc, and RBC counts Not carcinogenic. LOEL = 250 ppm</p>
4,4'-butylidenebis(6-t-butyl-m-cresol) (85-60-9)	90-day feeding study in rats - Increased liver weights, effects on SGOT and SGPT. Microscopic changes in liver and lymph nodes. NOAEL = 100 ppm; LOAEL = 500 ppm	ND
phenol, 4,4'-(1-methylethylidene)bis[2-(1,1-dimethylethyl)]-, (79-96-9)	ND	ND
phenol, 2,2'-methylenebis(4-methyl-6-nonyl) (7786-17-6)	ND	ND

ND - no data found

N = Non-sponsored chemical; used for data purposes only

**Table 7.**  
**Matrix of Available and Adequate Data for the Bridged Alkyl Phenols Category**

**Reproductive and Developmental Toxicity**

Name (CAS No.)	Reproductive	Developmental
2,6-di-tert-butyl-p-cresol (128-37-0)	<p>2-Generation in rats at 25 to 500 mg/kg/day (F0) and 25 and 250 mg/kg/day (F1)</p> <p>2-Generation in mice - Increased wt of pups at birth and during lactation. NOEL not established. LOEL=22.5 mg/kg/day</p>	<p>Mice by gavage - NOAEL for maternal tox = 240 mg/kg/day and NOAEL for terata &gt;= 800 mg/kg/day.</p> <p>Rat teratology, not teratogenic from two publications from Japan</p>
4,4'-thiobis-6-(t-butyl-m-cresol) (96-69-5)	<p>Histopathology of sex organs from chronic toxicity study in rats. No adverse effects observed.</p> <p>NTP postnatal mouse screening test. One dose = 485 mg/kg/day. Increased maternal mortality, decreased pup survival</p>	Developmental in rabbits - Maternal NOEL = 0.2 mg/kg/day. Effects on fetuses only at maternally toxic doses.
4,4'-butylidenebis(6-t-butyl-m-cresol) (85-60-9)	Histopathology of sex organs from 90-day repeated dose study in rats. No adverse effects noted.	ND
phenol, 4,4'-(1-methylethylidene)bis[2-(1,1-dimethylethyl)]-, (79-96-9)	ND	ND
phenol, 2,2'-methylenebis(4-methyl-6-nonyl) (7786-17-6)	ND	ND

ND - No data found

N = Non-sponsored chemical; used for data purposes only

**Legend for Table 8**

<b>Symbol</b>	<b>Description</b>
A	Endpoint requirement fulfilled with adequate existing data
NA	Not applicable due to physical/chemical properties
C	Endpoint requirement fulfilled based on calculated data
R	Endpoint requirement fulfilled using category approach, SAR

**Table 8.**  
**Bridged Alkyl Phenols Category Test Plan**

**Physicochemical Properties**

Name (CAS No.)	Melting Point	Boiling Point	Vapor Pressure	Water Solubility	Partition Coefficient
2,6-di-tert-butyl-p-cresol (128-37-0)	A	A	A	A	A
4,4'-thiobis-6-(t-butyl-m-cresol) (96-69-5)	A	NA	A	A	C
4,4'-butylidenebis(6-t-butyl-m-cresol) (85-60-9)	A	NA	C	A	C
phenol, 4,4'-(1-methylethylidene)bis[2-(1,1-dimethylethyl)]-, (79-96-9)	C	A	C	R	C
phenol, 2,2'-methylenebis(4-methyl-6-nonyl) (7786-17-6)	C	C	C	R	C

**Environmental Fate**

Name (CAS No.)	Hydrolysis	Photo-degradation	Bio-degradation	Environmental Transport
2,6-di-tert-butyl-p-cresol (128-37-0)	NA	A	A	A
4,4'-thiobis-6-(t-butyl-m-cresol) (96-69-5)	A	C	A	C
4,4'-butylidenebis(6-t-butyl-m-cresol) (85-60-9)	NA	C	A	C
phenol, 4,4'-(1-methylethylidene)bis[2-(1,1-dimethylethyl)]-, (79-96-9)	NA	C	R	C
phenol, 2,2'-methylenebis(4-methyl-6-nonyl) (7786-17-6)	NA	C	R	C

**N** = Non-sponsored chemical; used for data purposes only



**Table 8 (continued).**  
**Bridged Alkyl Phenols Category Test Plan**

**Ecotoxicity**

<b>Name (CAS No.)</b>	<b>Acute Fish</b>	<b>Acute Invertebrate</b>	<b>Algal Growth Inhibition</b>
2,6-di-tert-butyl-p-cresol (128-37-0)	A	A	A
4,4'-thiobis-6-(t-butyl-m-cresol) (96-69-5)	A	A	A
4,4'-butylidenebis(6-t-butyl-m-cresol) (85-60-9)	A	A	A
phenol, 4,4'-(1-methylethylidene)bis[2-(1,1-dimethylethyl)]-, (79-96-9)	R	R	R
phenol, 2,2'-methylenebis(4-methyl-6-nonyl) (7786-17-6)	R	R	R

**Acute Toxicity**

<b>Name (CAS No.)</b>	<b>Acute Oral</b>	<b>Acute Dermal</b>
2,6-di-tert-butyl-p-cresol (128-37-0)	A	A
4,4'-thiobis-6-(t-butyl-m-cresol) (96-69-5)	A	A
4,4'-butylidenebis(6-t-butyl-m-cresol) (85-60-9)	A	A
phenol, 4,4'-(1-methylethylidene)bis[2-(1,1-dimethylethyl)]-, (79-96-9)	R	R
phenol, 2,2'-methylenebis(4-methyl-6-nonyl) (7786-17-6)	R	R

N = Non-sponsored chemical; used for data purposes only

**Table 8 (continued).  
 Bridged Alkyl Phenols Category Test Plan**

**Genotoxicity**

Name (CAS No.)	Bacterial Gene Mutation	Chromosomal Aberrations	
		In vitro	In vivo
2,6-di-tert-butyl-p-cresol (128-37-0)	A	A	A
4,4'-thiobis-6-(t-butyl-m-cresol) (96-69-5)	A	A	A
4,4'-butylidenebis(6-t-butyl-m-cresol) (85-60-9)	A	A	R
phenol, 4,4'-(1-methylethylidene)bis[2-(1,1-dimethylethyl)]-, (79-96-9)	R	R	R
phenol, 2,2'-methylenebis(4-methyl-6-nonyl) (7786-17-6)	R	R	R

**Repeated dose Toxicity**

Name (CAS No.)	Subchronic Toxicity	Chronic Toxicity
2,6-di-tert-butyl-p-cresol (128-37-0)	A	A
4,4'-thiobis-6-(t-butyl-m-cresol) (96-69-5)	A	A
4,4'-butylidenebis(6-t-butyl-m-cresol) (85-60-9)	A	
phenol, 4,4'-(1-methylethylidene)bis[2-(1,1-dimethylethyl)]-, (79-96-9)	R	
phenol, 2,2'-methylenebis(4-methyl-6-nonyl) (7786-17-6)	R	

N = Non-sponsored chemical; used for data purposes only

**Table 8 (continued).**  
**Bridged Alkyl Phenols Category Test Plan**

**Reproductive and Developmental Toxicity**

<b>Name (CAS No.)</b>	<b>Reproductive</b>	<b>Developmental</b>
2,6-di-tert-butyl-p-cresol (128-37-0)	A	A
4,4'-thiobis-6-(t-butyl-m-cresol) (96-69-5)	A	A
4,4'-butylidenebis(6-t-butyl-m-cresol) (85-60-9)	A	R
phenol, 4,4'-(1-methylethylidene)bis[2-(1,1-dimethylethyl)]-, (79-96-9)	R	R
phenol, 2,2'-methylenebis(4-methyl-6-nonyl) (7786-17-6)	R	R

N = Non-sponsored chemical; used for data purposes only